



Gustave L. and Janet W. Levy
Library of Mount Sinai



Digitized by the Internet Archive
in 2015

**JOURNAL OF
THE MOUNT SINAI
HOSPITAL**

VOLUME XXXVI

1969

CONTENTS OF VOLUME XXXVI

NUMBER 1, JANUARY-FEBRUARY, 1969

	PAGE
OBITUARY: DR. ALVIN ARKIN.....	1
THE RELEVANCE OF MORPHOLOGY IN MEDICINE. <i>Hans Popper, M.D.</i>	3
AORTIC ANEURYSM INFECTED WITH KLEBSIELLA PNEUMONIA, SEROTYPE 1: A CASE REPORT. <i>S. Stanley Schneierson, M.D., and Edward Bottone, M.S.</i>	10
NEPHROTIC SYNDROME IN MYELOMA WITH AMYLOIDOSIS. <i>Thomas Kahn, M.D., Jacob Churg, M.D., and Marvin H. Goldstein, M.D.</i>	15
SEVERE HYPOXEMIA IN AN OBESE PATIENT WITH POLYCYTHEMIA VERA. <i>E. Leslie Chusid, M.D., Albert Miller, M.D., and Ralph Zalusky, M.D.</i>	21
REVERSIBLE GRANULOCYTOPENIA IN A PATIENT WITH POLYCYTHEMIA VERA TAKING NITROFURANTOIN: REPORT OF A CASE. <i>Stuart B. Levy, M.D., Burt Meyers, M.D., and Harold Mellin, M.D.</i>	26
PERIPELVIC URINE GRANULOMA—CASE REPORT. <i>Steven Alexander, M.D., Ruth Schwarz, M.D., and Harold J. Sobel, M.D.</i>	30
NEUROLOGIC MANIFESTATIONS OF NEUROBLASTOMA. <i>Jack Alpert, M.D., and Robert Mones, M.D.</i>	37
MULTIPLE MYELOMA INVOLVING THE EXTRAHEPATIC BILIARY SYSTEM. <i>Arthur B. Abt, M.D., and Ludwig M. Deppiseh, M.D.</i>	48
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i> AZOTEMIA, PROTEINURIA, PERIPHERAL VASCULAR DISEASE, AND FIBRO- THORAX IN A MALE WITH MILD DIABETES MELLITUS.....	55
UNUSUAL PROBLEMS IN SURGERY. <i>A. Robert Beck, M.D., Lewis Burrows, M.D., and Julius J. Leichtling, M.D., Editors</i>	
HENOCH-SCHÖNLEIN PURPURA.....	65
STUDIES IN BULLOUS DISEASES: TREATMENT OF PEMPHIGUS VULGARIS WITH METHOTREXATE, TWO PATIENTS (ONE WITH CONCOMITANT MYASTHENIA GRAVIS). <i>Samuel M. Peck, M.D., and Kermit E. Osserman, M.D.</i> ...	71

NUMBER 2, MARCH-APRIL, 1969

CURRENT THERAPY OF CYSTINURIA. <i>Howard J. Goldman, M.D., and Stanley I. Glickman, M.D.</i>	79
THE OCCURRENCE OF TYPE B-WOLFF-PARKINSON-WHITE CONDUCTION IN THE PRESENCE OF RIGHT BUNDLE BRANCH BLOCK. <i>Stephen Richmond, M.D., and Leon Pordy, M.D.</i>	96
EXPERIMENTAL TERATOGENESIS IN FERRETS USING RUBELLA VIRUS. <i>Teresita S. Elizan, M.D., Akinyele Fabiyi, Ph.D., and John L. Sever, M.D., Ph.D.</i>	103
STUDY OF RUBELLA VIRUS AS A TERATOGEN IN EXPERIMENTAL ANIMALS: A SHORT REVIEW. <i>Teresita S. Elizan, M.D., Akinyele Fabiyi, Ph.D., and John L. Sever, M.D., Ph.D.</i>	108

HYPOKALEMIA, METABOLIC ACIDOSIS, AND HYPOCALCEMIC TETANY IN A PATIENT TAKING LAXATIVES. A CASE REPORT. <i>Paul Goldfinger, M.D.</i>	113
POTASSIUM DEPLETION AND METABOLIC ALKALOSIS IN A PSYCHIATRICALY DISTURBED PATIENT. A CASE REPORT. <i>Paul Goldfinger, M.D.</i>	117
CEREBELLAR GLIOBLASTOMAS. <i>Sidney W. Gross, M.D., Richard Cohen, M.D., and Songsant Panichavantana, M.D.</i>	123
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i>	
POLYCYTHEMIA AND TRANSIENT HYPOGLYCEMIA IN A 77-YEAR OLD MALE . .	130
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey Peck, M.D., Co-Editors</i>	
HEMATOMA OF THE LARYNX	145
HEREDITARY ONYCHO-OSTEODYSPLASIA	150
ABNORMAL AXIS OF LABOR FORCES DUE TO LAXITY OF THE ABDOMINAL WALL	155
DISTENDED URINARY BLADDER IMPEDING PASSAGE OF THE FETAL HEAD . .	156
DEMONSTRATION OF THE RENAL FASCIA	158
TRAUMATIC VERTEBRAL ARTERIOVENOUS FISTULA	160
POST-TRAUMATIC ARTERIOVENOUS FISTULA BETWEEN CAROTID ARTERY AND OPHTHALMIC VEIN	164

NUMBER 3, MAY-JUNE, 1969

MEDICINE IN A CHANGING WORLD. <i>Dr. George W. Beadle</i>	171
MOLECULAR BIOLOGY AND MEDICAL RESEARCH. <i>Dr. Francis H. C. Crick</i> . .	178
GENETICS AND THE MEDICINE OF THE FUTURE. <i>Sir Peter Medawar</i>	189
MEDICINE IN A RATIONAL SOCIETY. <i>Dr. Linus Pauling</i>	194
THE USE OF VALVE HOMOGRAFTS IN CARDIAC SURGERY. <i>Paul Marchand, M.D.</i>	200
CARPAL TUNNEL COMPRESSION SYNDROME: UNUSUAL CASE REPORTS. <i>Angela A. Ramirez-Irizarry, M.D., and Leon Bluestone, M.D.</i>	210
PANCREATIC ASCITES. CASE REPORT: ASCITIC FLUID LIPASE UTILIZED FOR DIAGNOSIS. <i>Robert B. Wagner, M.D., and Stephen H. Tolins, M.D.</i> . .	216
MESENTERIC VASCULAR OCCLUSION. <i>Raghavendra Vijayanagar, M.D., Stephen H. Tolins, M.D., and Philip Cooper, M.D.</i>	220
UNUSUAL PROBLEMS IN SURGERY. <i>A. Robert Beck, M.D., and Julius J. Leichtling, M.D., Co-Editors</i>	
RECURRENT SACROCOCCYGEAL TERATOMA WITH RECTAL FISTULA	227
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i>	
GASTROINTESTINAL BLEEDING	236

NUMBER 4, JULY-AUGUST, 1969

OBITUARY: DR. SADA O OTANI	245
SELECTED EXPERIENCES WITH CARDIAC PACING. <i>Philip Samet, M.D., and John W. Lister, M.D.</i>	248
CANCER OF THE NASOPHARYNX: A STUDY OF NINETY CASES. <i>Samuel M. Bloom, M.D.</i>	277

HEMANGIOMA AS A CAUSE OF CRYPTOGENIC GASTROINTESTINAL HEMORRHAGE. <i>Jose C. Cacatian, M.D., and Milton Kannerstein, M.D.</i>	299
ACUTE APPENDICITIS PRESENTING AS MULTIPLE, EXTRA-ABDOMINAL ABS- CESSSES. <i>Stephen A. Geller, M.D.</i>	308
NEUROLOGIC SYNDROMES ASSOCIATED WITH PRIMARY THROMBOCYTHEMIA. <i>Gary Korenman, M.D.</i>	317
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Co-Editors</i>	
ISCHEMIC COLITIS: PRESENTATION OF SEVEN CASES	324

NUMBER 5, SEPTEMBER-OCTOBER, 1969

OBITUARY: DR. MARTIN C. ROSENTHAL	345
CURRENTS IN MEDICAL EDUCATION IN THE UNITED STATES. <i>Hans Popper, M.D., Ph.D.</i>	348
THE INITIATING CAUSE OF CORONARY ARTERY THROMBOSIS: AN ANATOMIC STUDY. <i>Irving Chapman, M.D.</i>	361
DISSEMINATED INFECTION BY MYCOBACTERIUM FORTUITUM. <i>Kalmen Alex Feinberg, M.D., and S. Stanley Schneierson, M.D.</i>	375
POLYMYXIN B-INDUCED RESPIRATORY PARALYSIS REVERSED BY INTRAVENOUS CALCIUM CHLORIDE. <i>Robert Aaron Lerine, M.D., in conjunction with Michael P. Beiber, M.D., Francis A. Forte, M.D., Steven P. Gersten, M.D., Mark E. Krugman, M.D., Norman Rosenstock, M.D., Herbert S. Sherry, M.D., and George A. Violin, M.D.</i>	380
PANCREATIC DISEASE: A REVIEW. <i>David A. Dreiling, M.D.</i>	388
INEFFECTIVENESS OF DIAZEPAM AS AN ANTIARRHYTHMIC AGENT. <i>Michael A. Nevins, M.D., Leonard M. Mattes, M.D., Ruth C. Spritzer, M.D., Arthur C. Weisenseel, M.D., Ephraim Donoso, M.D., and Charles K. Friedberg, M.D.</i>	408
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i> ANEMIA, AZOTEMIA, AND RECTAL BLEEDING IN A MIDDLE-AGED FEMALE	415
RADIOLOGICAL NOTES. <i>Claude Bloch, M.D., and Harvey M. Peck, M.D., Co-Editors</i>	
DERMOID CYST OF THE OVARY VERIFYING OVARIAN MOBILITY DURING PREG- NANCY	423
"PRUNE-BELLY" SYNDROME	425
BENIGN NODULAR LYMPHOID HYPERPLASIA OF THE SMALL BOWEL. <i>Discussed by Rhona J. Keller, M.D.</i>	430
SMALL BOWEL APPEARANCE IN ANAPHYLACTOID PURPURA	434
HYPERNEPHROMA WITH MASSIVE PERIRENAL HEMATOMA. <i>Submitted by Melvin R. Sherach, M.D.</i>	439
AFTERLOADING MULTIPLE IRRADIATORS FOR THE TREATMENT OF CANCER OF THE CORPUS OF THE UTERUS: A PRELIMINARY REPORT OF A NEW DE- VICE. <i>Norman Simon, M.D.</i>	443

NUMBER 6, NOVEMBER-DECEMBER, 1969

OBITUARY: DR. ROBERT K. LIPPMANN.....	447
OBITUARY: DR. ARTHUR SCHIFRIN.....	451
THE HEALTH OF THE FETUS DURING LABOUR. <i>Stanley G. Clayton</i>	454
TOLBUTAMIDE IN PREGNANCY AND DIABETES. <i>Henry Dolger, M.D., John J. Bookman, M.D., and Charles Nechemias, M.D.</i>	471
CARDIAC TRANSPLANTATION IN MAN: ITS THERAPEUTIC AND OTHER IMPORTANCE. <i>Denton A. Cooley, M.D.</i>	475
CARDIAC ARRHYTHMIAS DUE TO HYPERSENSITIVITY: A REPORT OF TEN CASES. <i>Joseph Harkavy, M.D.</i>	485
THE PSYCHIATRIST LOOKS AT MEDICAL PROGRESS. <i>M. Ralph Kaufman, M.D.</i>	497
A SHORT-TERM EVALUATION OF L-DOPA THERAPY IN 34 PATIENTS WITH PARKINSONISM. <i>R. J. Mones, M.D., and T. S. Elizan, M.D.</i>	503
CLINICO-PATHOLOGICAL CONFERENCE. <i>Franklin M. Klion, M.D., Editor</i>	
ANASARCA AND COMA IN A YOUNG MALE.....	516
INDEX TO VOLUME XXXVI.....	527

In Memoriam

ALVIN ARKIN, M.D.

1912-1968

The sudden death of Dr. Alvin Arkin bewildered his friends, his patients, and his colleagues, for they were unaware of his illness which he bore so gallantly for twelve years. He burdened no one, not even his loved ones, but ear-



ALVIN ARKIN, M.D.

1912-1968

ried on his practice nobly. Those of us who knew Alvin Arkin at Columbia College, New York University College of Medicine, and Israel Zion Hospital (now the Maimonides Hospital), will remember his bright sparkling humorous

personality. It was always a pleasure when Alvin entered the scene. At the Orthopedic Departments of Bellevue, the University of Iowa, and The Mount Sinai Hospital where he trained, he soon made a reputation for his high professional competence, his imaginative mind, his good heart, and his extra touch of the cultured gentleman. His interests outside his profession were manifold and included sailing, photography, travel, and reading. An omnivorous reader, he covered an amazingly wide range of subjects. He made original contributions in the field of orthopedics dealing with Gaucher's disease, experimental work on pressure and growth, and scoliosis. Unfortunately, his insidious, progressive, chronic disease subdued his natural energy and prevented the fulfillment of his contributions to the knowledge of scoliosis. To the very end of his fifty-eight years, he was a loving and tender husband, superior and kind orthopedist and a gay personality who appreciated and enjoyed his work and life. His wife, Ann and three children, Norma, Elizabeth, and John survive him.

JOEL HARTLEY, M.D.
for the
EDITORIAL BOARD

The Relevance of Morphology in Medicine

HANS POPPER, M.D., Ph.D.*

As we inaugurate our new school we should 1) briefly look back on the events which have made world medicine what it is, 2) understand the presently increasing contribution of America to the reconciliation of medical hard science, that is basic and clinical research, with the attempt to spread its benefits all over the population, and 3) refer to the heritage of Mount Sinai Hospital which forms the concept of this new school. The most intensive view, however, should be directed to the medicine of the future with its today unknown demands and opportunities. We know that all of us, and particularly and fortunately so, the younger of us, are questioning the relevance of today's teaching to the known, the predictable, and particularly to the unknown demands of the practice of medicine in the last quarter of this century and in the beginning of the next century when you will have to do justice to these demands.

Traditionally, since the time of Hippocrates and especially since the great physicians of the Italian schools, the medical student has based his initial studies upon anatomy and the dissection of the human body. The rostrum of the anatomic amphitheater in the famous University of Bologna, the oldest of the still existing medical schools of the world, carries the Latin inscription *HIC LOCUS EST UBI MORS GAUDET SUCCURERE VITAE* translated "Here is the place where death enjoys to serve life." Some of you may know that the same inscription can still be seen in the old autopsy room at Mount Sinai Hospital, soon to be demolished to give way to the new Annenberg building of our new school. How relevant is anatomy and the observation and study of form or shape in general, in short morphology, to the future practice of medicine? This challenging question has been raised since the beginning of this century which has seen the rapid development of the study of forces, of physiology and biophysics, and of the application of chemistry to biologic phenomena. Let us try to answer it.

To appreciate the relevance of morphology to today's and to the future practice of medicine, let us look at our principal approach. Here we deal primarily with two aspects, that of the patient as a person and that of his disease. In the first we are interested in his mind and his relation to society as a whole. We study his impact upon the community and the community's impact upon him. There may be a conflict in our attention between the patient as a whole and his disease, a conflict which may be potentially detrimental, because here is where the present revolution of relevance previously referred to may come in. However, at the very beginning of your medical studies it should be stressed that

Opening lecture given to the first year students in the new Basic Science Building of the Mount Sinai School of Medicine on September 9, 1968.

* Dean for Academic Affairs, Given Foundation Professor, and Chairman, Department of Pathology, Mount Sinai School of Medicine of the City University of New York, New York, N. Y.

as physicians, you will have to live with conflicts, with polarities that we are reconciling with "a spectrum of values." When we turn to the problem of the disease we are trying to do two things. The first is to recognize the disease including its precursor stages which may not be clinically apparent. The second is to manage the disease which includes the prevention of the clinical, disabling state in the precursor condition. In both these attempts we desire information which lets us develop predictable rules. Both attempts have been based, again since Hippocrates, (and even since the physicians in preceding civilizations like the Egyptians and Chinese, the heritage of which is less well known to us), upon two different approaches. The first is the collection of empirical observations which record coincidences without knowing why these patterns occur. Much of what we are teaching today and what we must remember as practicing physicians, is based on these empirical coincidences even if we now establish and recognize patterns by computers. Our other effort is the scientific approach which again may be subdivided into two types of endeavor. The first is the quantitative expression of observations as well as the refinement of the observations by ever more complex morphologic techniques, such as light and electron microscopy, by physical measurement, and by chemical analysis. This quantitation is applied to animals and men, including the patients at the bedside and also to the psychological behavior of population groups. Essentially this scientific method still remains a recording of observations, a description of functional and structural parameters. To make it meaningful we attempt a correlation of these observations, whether they be anatomic, functional, or clinical. We choose by intuition one of several possible answers. But correlation never proves causal relation. This synthetic but still hypothetical approach makes possible the delineation of disease entities, an endeavor in which Mount Sinai Hospital has been particularly successful in its past. Again statistics may make these correlations more predictable. Better quantitation by increasing sophistication of measurement and their better correlation through cybernetic techniques promises us a great future in this approach but also the curse of an overabundance of facts hard to retain by a single man.

The second subdivision of this scientific approach is inductive reasoning, for which Francis Bacon is given credit for first verbalizing it. This is the experimental method which, if we organize it right, should give one correct answer from two possibilities. This is strong inference and hard science. Molecular biopsy has recently shown ingenious examples of asking the right questions and of inductive reasoning. Such experiments are performed by the investigator in his research or by the student in his studies, but for the physician experiments of nature are equally rewarding. A good example is the genetically induced lack of a single enzyme, which results in a characteristic structural and functional alteration, a defined human disease. This serves to develop predictable principle applicable to understanding and managing many diseases.

What we then have to teach and learn together are 1) empirical experiences, 2) observations by various techniques meticulously applied and as well correlated as we can to come to a meaningful synthesis, and 3) inductive or ana-

lytical science, whether such science is the science basic to medicine and conducted in this building, whether it is the newly developing clinical sciences using the same techniques in the hospital, whether it is psychobiology conducted on animals but also on man gradually applying the methods of clinical science, even in mental institutions, or whether it is social biology which is the attempt to use hard science and strives for predictability in the study of the population at large in community medicine.

Thus empirical observation and quantitative description provide us with facts while correlation and experiment give us, hopefully, principles. These principles in turn may help us understand and thus better remember the facts. In all these endeavors in which we always attempt to distill principles from facts, whether we deal with a cell, an organ, a human being or population groups, morphologic description has been essential. It even enters in the understanding of the now so emphasized urban problems. For example, experiments have shown that crowding animals in cages creates distinct changes in the so-called pituitary-adrenal axis which we establish by careful morphologic analysis.

One of the oldest means to study the human body is to use morphology, particularly gross anatomy, as a predictive tool. For instance, the Egyptians measured the dissected heart to learn about the psyche. And the study of the lobulation of the liver goes back about 4000 years. A Babylonian sheep liver is illustrated in stone in the British Museum in London. It shows well the lobulations of the organ and this picture compares favorably with illustrations of the lobulations in modern textbooks. They show them to assist the surgeon who wishes to resect parts of the liver. Yet Babylonian seers studied the lobulation of the liver in sacrificial animals to predict the future. On an ancient Etruscan vase we see the seer, who is called *haruspex*, predicting for the king *Adrastus*, ready to go into the Theban War, the outcome of this war before its start by using the lobulation of the liver of a sacrificial animal. It is worth remembering that we often make *haruspicial* predictions based on superstition in medicine even if we look at the liver with the electron microscope and believe that an abnormality recorded has a functional, that means predictive, significance, only to learn later that the assumed correlation is not better than that between the Etruscan War and the lobules of the animal liver.

Nevertheless, many predictions and correlations proved to be more valid, particularly when human dissection became the basis of normal and pathological anatomy and particularly when it was developed as a basis for the understanding of diseases. Still, in the thirteenth century Italian anatomists published pictures based on Arabian studies which show the portal vein bringing air to the liver while the spleen secretes the bile into the stomach. Eventually anatomic dissection, particularly in the amphitheatres of the classical Italian school, was effectively correlated with clinical observations. Boerhave in Leyden introduced bedside teaching. These combined successes culminated in a famous treatise by Giovanni Morgagni appearing in 1791 called "*De sedibus et causis morborum per anatomen indagatis*" (the localization and causes of

diseases studied by anatomy). Since then the microscope became available and provided additional support which was reflected in the classical studies of Malpighi of Bologna whose name is attached to so many anatomic structures. The famous clinicians of the French and English schools of the 18th and early 19th centuries combined anatomical dissections with clinical observations and the names of Hunter, Hodgkin, Bright, Addison, and Laennec are household words in medicine.

Yet by the end of the 19th century, it appeared that most of the morphologic observations possible in man and those relevant in animals seemed to have been made. Normal and abnormal morphology which had been until then the basis of medicine was losing its relevance to medical progress, though not necessarily to medical teaching and practice. This coincided with an almost explosive progress in the study of forces instead of shapes, of physiological processes, and of chemical reactions. All this was called "study of function" or dynamic investigation. Processes of regulation, of disturbed homeostasis, of humoral alterations determined in the serum, became the predictive basis of disease. These factors were, at most, inadequately expressed in altered shape. Biochemical and functional causes of disease and even of death were fully accepted.

The well defined lines of classical morphology comparable to the classical lines of the Greek temples of antiquity were replaced by ingenious, but unrestrained considerations with the sky as the limit, comparable to the spires of Gothic cathedrals. In this century, however, a renaissance of morphology set in, yet just as the Renaissance did not take place in Greece, but expressed itself in the Italian and French palaces, so the relevance of morphology was discovered not in the old anatomic sciences but initially in atomic and nuclear physics, started by Dalton's thoughts in 1915, which replaced Newton's classical physics. Only in the early Forties, when nuclear physics blossomed, did the scientific world reemphasize that shape determines the activity of forces. The reborn morphology moved from physics to molecular biology. The shape seen in x-ray defractions led to the discovery of the helix shape of DNA. Biological morphology thus allowed a breakthrough in genetics. Biologic electron microscopy began in virology but it has gradually come to both the classical morphologic disciplines, anatomy and pathology. It produced a new bloom in the old quarters, particularly when chemical analysis of cell fractions identified by electron microscopy gave meaning to the submicroscopic or fine structural details seen under the electron microscope. On this fine structural level structure and function merge. The biochemist came to realize that localization may mean more than chemical analysis of the whole organ which latter has been compared with the attempt to understand the principle of a building, after its demolition, by thorough investigation of the rubble. Thus morphology identifies the processes taking place at the interphase within the cells, between cells, between organs, and between men. At present the membrane or interphase processes are in foreground of our interest and they guarantee relevance of morphology even if the present morphologic clinical and laboratory techniques should be entirely replaced by ingenious objective measurements.

A unity of biology has emerged out of the old conflict between structure and function. This unity will be the keynote of our teaching. It is illustrated in the chemical and physical analysis of the organelles, visible cell constituents with defined function for the organism as a whole and for the household of the cell. Study of these organelles teaches us much about cellular physiology, about biochemistry, and about anatomy. Such study at the same time blurs the borders between these classical disciplines. Since we are often studying the effect of drugs on these organelles pharmacology is entering this unified pool of biology.

The term "unity of biology" also implies that structural and functional characteristics of microorganisms including viruses have significance. Not only do we describe them for diagnosis of disease, but even more so we try to understand their effect on man. In addition they serve as simple models of processes which can be better studied in them than in the more complex mammalian cells. Many of the findings of molecular biology have been developed in virus and in bacteria, for example, the regulation of DNA synthesis and the processes regulating cell renewal. A classic experiment is the induction of the enzyme galactosidase in bacteria by the introduction of its substrate galactose into the culture medium. Only recently have we learned about the regulatory forces in whole organs or whole cells, the latter for instance, by studies in cell culture.

The study of abnormal reactions, pathology, also enters into the unity of biology. By looking at the whole man or by gross dissection of organs, our ancestors had little difficulty separating normal from abnormal. It is far more difficult for our generation. Careful anatomical measurements, including gross or histological characteristics, have obscured what normality means. For instance, on administration of some drugs the liver enlarges without gross and light microscopic changes, but one organelle of the liver cell is increased in amount, namely the agranular endoplasmic reticulum which is a system of tubular profiles in the cytoplasm. At the same time the animal or man becomes better able to handle drugs. This means a larger amount of drugs has to be given to obtain a given effect. This enzyme induction and liver enlargement is an aberration from the norm, but it is itself not a disease, but possibly it might render the individual susceptible to diseases. We thus see that we cannot draw a sharp line between the normal and the pathological state and thus, especially on the fine structural level, pathological considerations enter the unity of biology.

Pathology as the study of the mechanism of disease developed similarly in relation to morphology. Originally pathology dealt with the morphologic basis of disease as recognized in the appearance of organs at autopsy conducted to detect the cause of death and the presence of disease, and of biopsy specimens establishing, for instance, the presence of cancer. Virchow, in the nineteenth century emphasized the dysfunction of the individual cell and created cell pathology. But in the same period, Rokitsansky, though himself a meticulous morphologist, introduced in visionary fashion the concept of alterations of fluids, humoral pathology. Since morphology seemed less relevant, the func-

tional defect not apparent in morphologic appearance, became important. Electrolyte imbalance, for instance excess of serum potassium, was thought more important than some uncharacteristic changes seen with the naked eye or with the light microscope. The renaissance of morphology in pathology received further impetus when several years ago Linus Pauling coined the term "molecular pathology" and pointed out that a single change in the amino acid sequence of hemoglobin as a result of an alteration in the DNA explains sickle cell disease. Today, however, molecular pathology has as yet limited application in clinical medicine. But, the recent rapid development of electron microscopy correlated with chemical, physical and even immunologic studies of cell fractions, coordinated functional and structural study, has led to the concept of a still embryonal organelle pathology which finds itself in the gap between the cellular pathology of Virchow and the molecular pathology of Pauling.

Changes in circumscribed organelles in the living cell may reflect structural and functional disorders. For instance, the granular endoplasmic reticulum of the hepatocytes is a system of narrow profiles in the cytoplasm lined by granules composed of RNA, the ribosomes, which are spirally arranged around a thread of messenger RNA. These ribosomes are responsible for the synthesis of the proteins which the liver cell secretes into the blood. Such proteins include serum albumin or the proteins involved in blood coagulation. One of the first alterations of the hepatocyte produced experimentally, for instance by poisons like carbon tetrachloride, or by disease, such as viral hepatitis, leads to a shattering of the endoplasmic reticulum and the detachment of the ribosomes. The still viable cell stops secreting the proteins mentioned above. We see here the morphologic basis of a functional change found in early liver disease and accounted for by the electron microscopic appearance of cells which are alive, which seem to be almost normal under the light microscope, but which have diseased organelles. Such a diffuse injury of live cells is more important than a histologically impressive necrosis or the disappearance of a few liver cells. These latter phenomena have interested the pathologist of the previous generation, but they need not have any significance since the liver has ample reserve capacity and the disappearance of a few cells may have no functional impact. Organelle pathology, limited dysfunction of live cells, is thus a biological phenomenon related to all the other sciences basic to medicine.

Pathology connects sciences basic to medicine and clinical medicine. It is an integrative science. It does not have its own technique and applies that of all other basic sciences. It is only partly a basic science, when as an analytic and experimental science, it strives to unravel the mechanism of disease by integrating morphologic and functional observations, whether it is organ pathology, cellular pathology, organelle pathology, or molecular pathology; whether it represents the emerging psychopathology or the hardly existing social pathology of the future which we have to develop into a hard science to contribute to the solution of the pressing problems of the world. However, pathology also is concerned with the etiology of diseases as well as with the tools to diagnose

disease and then it represents clinical practice. Finally, it studies the rationale of effective therapy and here it is a clinical science.

The presented theme of unity of biology has pragmatic implications for much of what we will do together in coming years. The theme is reflected in the attempt to develop principles rather than facts, principles which have an inherent logic while facts have to be memorized, crucial as they may be in the recognition and management of diseases, as long as coincidence rather than causal relations prevail in medicine. The appreciation of the principles is also important because they prepare us better for the constant change in medicine with which you will have to live by absorbing the changes during your professional lifetime. The theme is reflected in our multidisciplinary laboratories, which disregard departmental borders. It is reflected in the integrated curriculum. After the initial block time devoted to departmental teaching, we will attempt to study together normal and abnormal organ structure and function and pathophysiologic processes. We hope also to reflect the unity of biology in the introduction to medicine where, at the bedside, we wish to convey to you the relevance of the basic sciences, but also to present there the non-biologic features of medicine and finally to give you ease in dealing with patients as persons and to examine them well by proper techniques. Most important however, another principle of our school prevails here, namely the separation of an essential core curriculum time which hopefully will give you facts, skills, and principles required of every physician, from an ample free curriculum or elective time for study in depth in one or several areas chosen by you since unity of biology permits ready application of one principle to other areas.

I have tried to make several points in this highly subjective discourse given by a pathologist who wishes to know as much as possible about one field, the liver. 1) I started with the approach to medicine as a whole; empiricism as well as correlative science result in synthesis and inductive or experimental science in analysis; all four tempered by the understanding of the individual and the community. 2) I emphasized the unity of biology in structure and function, in the techniques applied in the laboratories, in the merging between normal and abnormal, and lastly in the principles common to man, animals, and microbes. 3) I spoke of pathology as a basic science, as clinical practice and as clinical science and 4) I discussed the relevance of morphology in biology and medicine not only as a tool of diagnosis but also as an inseparable partner of functional study. A fifth point, which I have not yet made in this lecture, is a personal one; as equals we shall travel a difficult but interesting road together. It is our desire, and I hope it is yours, that we complete the journey together with all of you. We want to be of assistance to you. The help, encouragement, and counsel which you will give us will let us help, encourage and counsel you better.

Received for publication September 23, 1968

Aortic Aneurysm Infected with *Klebsiella Pneumoniae*, Serotype 1

Case Report

S. STANLEY SCHNEIERSON, M.D., AND EDWARD BOTTONI, M.S.

A review of the literature concerned with infected aortic aneurysms covering 34 cases recorded in the world literature, all but eight since 1957, has been recently reported upon by Bennett and Cherry (1). Bacterial genera and species involved as evidenced by positive cultures have been *Salmonella* predominantly (2-12), other Gram negative bacilli such as *Escherichia coli* and *B. proteus* (6), *Staphylococcus* (1), *Neisseria gonorrhoeae* (13, 14), *Diplococcus pneumoniae* (15) and *Streptococcus* (16). In a number of instances cultures were not obtained and diagnosis was based upon microscopic observation of Gram positive cocci (17-21) or Gram negative bacilli (6) in sections of the involved aneurysms. In some cases, no bacterial identification was made either culturally or morphologically (9, 19, 22-25).

The present report is concerned with a case in which a hitherto unreported bacterial species, namely *Klebsiella pneumoniae*, Type 1, was cultured from the wall and contents of a resected aneurysm of the abdominal aorta, as well as from surrounding abscesses.

Case Report

The patient, a Negro man, 68 years of age, was admitted to The Mount Sinai Hospital Service of the City Hospital Center at Elmhurst with a chief complaint of abdominal pain of four days' duration and cramps in both legs. He was a known hypertensive for 17 years. Ten years prior to admission, the patient had had episodes of epigastric pain, and a duodenal ulcer was demonstrated by x-ray. He was placed on intermittent antacid therapy with generally satisfactory results. Four years ago, he again experienced epigastric pains and at the same time intermittent claudication of both legs which progressed to the point of incapacitation. Four days prior to admission, the epigastric pain became more severe with radiation to the back and he was admitted with a provisional diagnosis of penetrating peptic ulcer.

On examination, the patient was conscious, coherent, and alert. His blood pressure was 190/105, temperature 100.8°F and pulse rate 90/min. Arcus senilis was observed in both eyes. Diminished chest expansion was noted on both sides and occasional crepitant rales were heard over both bases. The heart was enlarged three fingerbreadths outside the midclavicular line, and a systolic murmur was heard at the apex as well as occasional ectopic beats. The abdomen was flat with guarding in the epigastric area and some tenderness on deep palpation. The lower abdomen was soft. Only the right femoral pulse could be palpated, the rest of the peripheral pulses were absent. There was no evidence of edema. Neurological examination was unremarkable.

Hemoglobin was 14.2 gm/100 ml. WBC 17,600/cu mm with 73% segmented forms. Hematocrit was 40%. Urinalysis revealed 1+ albuminuria, and 8-20 wbc/hpf, and tests for glucose and acetone were negative. Blood urea nitrogen was 26 and glucose 130 mg/100 ml. Chest x-ray revealed the cardiac silhouette to be enlarged mainly to the left with

From The Department of Laboratories, Mount Sinai Hospital Service, City Hospital Center at Elmhurst, Queens, New York.

some right ventricular hypertrophy as well. The aorta was dilated and tortuous. The pulmonary arteries were not overly prominent and there was no evidence of pneumonic infiltration or effusion. EKG revealed regular sinus rhythm with premature ventricular contractions, marked left axis deviation, left atrial and left ventricular hypertrophy and was interpreted as indicative of a possible old antero-septal myocardial infarction.

Epigastric pain persisted for the first eight hospital days and was unrelieved by antacids. He had moderately high leukocytosis and low grade temperature ranging from 99° to 101° F. Repeated flat plates of the abdomen failed to demonstrate aortic calcification. Because of the persistence of abdominal pain, the patient was reevaluated and a pulsatile mass in the epigastric region, that had been previously missed because of guarding, became evident.

A laparotomy was performed and operation revealed an aortic aneurysm with abscesses both within and outside the aortic wall. It measured 10 cm in length and included the abdominal aorta below the renal arteries extending to the bifurcation and involving the left common carotid artery. The aneurysm was resected, and smears and cultures were immediately obtained from the infected sites. Because of the presence of a small, firm, palpable duodenal mass as well, gastrostomy was considered advisable and was performed. Postoperatively, 0.5 gm of streptomycin was administered twice daily as well as cephalothin 1 mg every six hours. The etiological organism subsequently isolated proved sensitive *in vitro* to both of these antimicrobial agents. 5,000,000 units of penicillin was also given daily.

On the 15th postoperative day, chocolate-colored discharge was seen around the gastrostomy tube and the gastrostomy aspiration also had a bloody color. Impression was that of erosion of the duodenal wall and the patient was brought back to the operating room for a second laparotomy. Multiple intraperitoneal abscesses were found between matted loops of small bowel and were drained. However, drainage of bile persisted and confirmation of the diagnosis of continued duodenal erosion was established by small bowel x-ray series through the gastrostomy tube. Five days following the second exploration, the patient was again brought back to the operating room. The fourth portion of the duodenum was found to be eroded with free flow of bile and intestinal contents. The involved part of the duodenum was resected and end-to-end anastomosis was carried out. During this procedure, the patient went into shock and despite massive blood and fluid transfusions, he expired eight hours following the third surgical procedure.

Gross examination of the aortic specimen resected originally revealed fragmentation of the aorta with multiple fragments of soft, pliable, hemorrhagic material resembling blood clots within the aneurysm. The intima manifested a considerable amount of plaque formation and organized blood clot. The wall was brittle and hard. Atherosclerotic deposits, cholesterol clefts free of calcification, and partially organized thrombi were noted microscopically in the fragments of the arterial wall as well as focal aggregates of acute inflammatory cells. Histological diagnosis was "fragments of arterial wall with severe atherosclerotic changes and acute inflammation."

Gram stain smears of the exudates obtained from within the aortic wall and from the surrounding abscesses at the first operation revealed the presence of numerous Gram negative bacilli, a number of which were distinctly capsulated (Fig. 1). A blood agar plate streak yielded highly tenacious, stringing, mucoid growth after incubation at 37° C for 24 hours (Fig. 2). The culture consisted of non-motile, capsulated Gram negative bacilli that were indole, methyl red and Voges-Proskauer negative, but citrate positive. Urease and hydrogen sulfide were not produced. Xylose, maltose, sucrose (late), mannitol (late), dulcitol, salicin and sorbitol were fermented; lactose and raffinose were not. Lysine decarboxylase was positive. Based upon its colonial growth, microscopic morphology and biochemical characteristics, the isolate was categorized as *Klebsiella pneumoniae*. Definitive identification was established by its positive Neufeld "Quellung" reaction with Type 1, *Klebsiella pneumoniae* antiserum (Fig. 3).

In order to establish a possible source for the aortic infection, repeated urine, stool,

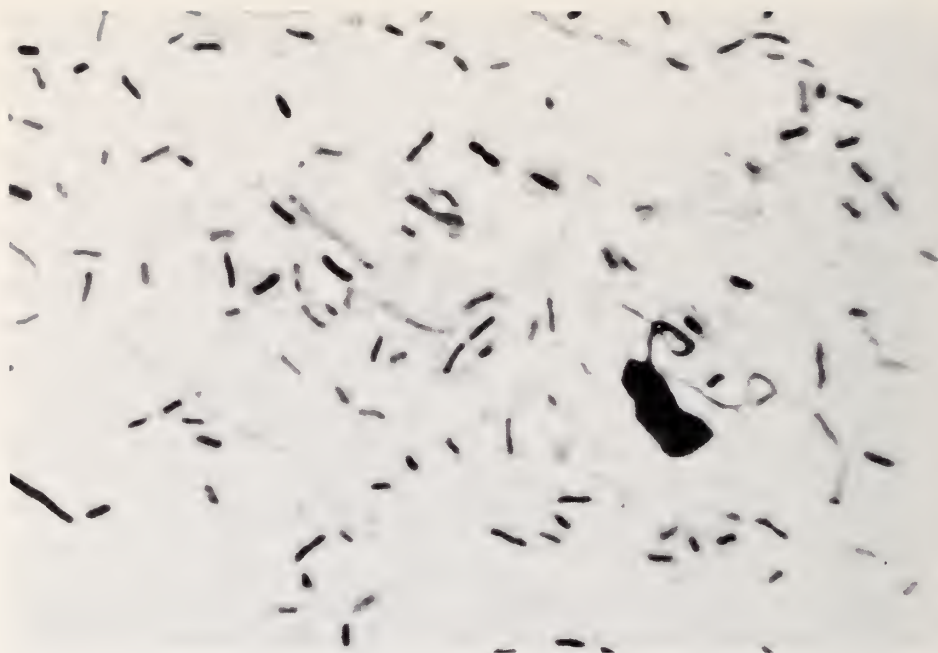


FIG. 1. Smear of abscess of aortic aneurysm. Numerous bacilli, many distinctly capsulated.

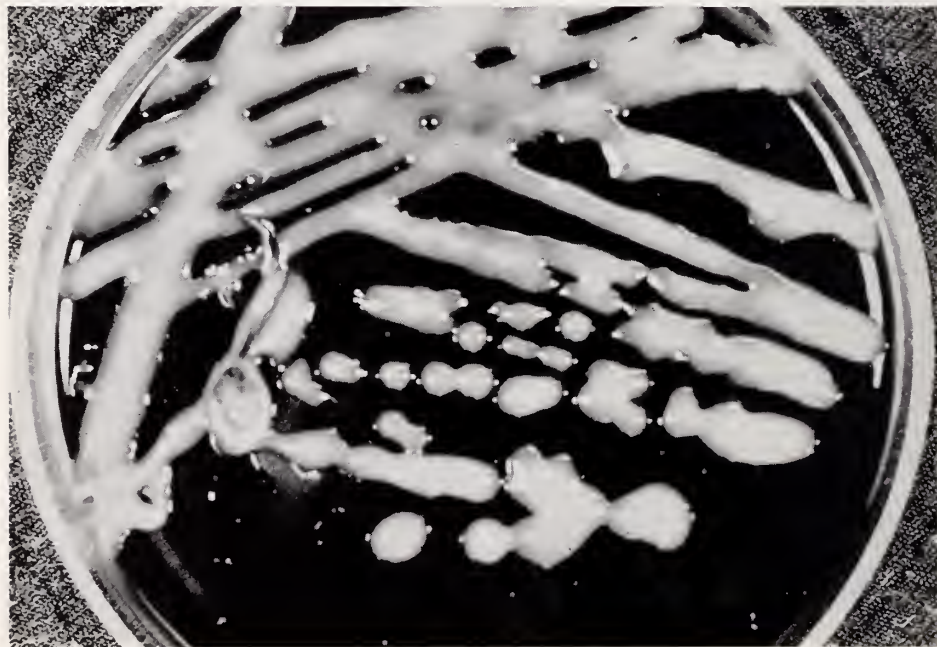


FIG. 2. Highly mucoid growth of culture of infected aortic aneurysm.



FIG. 3. Capsular swelling of isolate with *Klebsiella pneumoniae*, Serotype 1 antiserum (Neufeld Quellung reaction).

and sputum cultures were performed, but all proved negative for the involved micro-organism.

Infection of an aortic aneurysm is an uncommon condition. Sommerville (19) reviewed 178 atherosclerotic aortic aneurysms and found only six with histological evidence of acute infection. Four of the latter ruptured and caused death as compared to only eighteen per cent of the remainder that suffered this complication. No particular clinical feature characterizes the presence of infection, but persistent fever in a patient with aneurysm is cause for suspicion. The source is usually difficult to establish. However, the presence within an atherosclerotic blood vessel of blood clots, which is an excellent medium, is undoubtedly contributory. In all probability, periodic transitory bacteremia with localization of the infecting organism in this highly susceptible focus plays a role. The prognosis is usually poor even when the infecting organism is susceptible to the antibiotic or antibiotics administered. This is in all probability due to failure of antibiotic penetration into the involved focus because of the pathological nature of the lesion.

Summary

A case of aortic aneurysm infected with a hitherto unreported bacterial species, namely *Klebsiella pneumoniae*, Serotype 1, is reported. Literature concerned with infected aortic aneurysm and the microorganisms involved is reviewed.

References

1. Bennett, D. A., and Cherry, J. K.: Bacterial Infections of Aortic Aneurysms. A Clinico-Pathologic study, *Am J Surg* 113:321, 1967.

2. Dehlinger, K. R.: Salmonella Osteomyelitis of the Spine Associated with Abdominal Aortic Aneurysm: Report of a Case, *New Eng J Med* 238:728, 1948.
3. Boshier, L. H., and Decker, A. M., Jr.: Experiences in Vascular grafting for Aortic and Arterial Aneurysms, *Ann Surg* 145:943, 1957.
4. Simon, S. D., and Silver, C. M.: Salmonella Osteomyelitis: Report of Three Cases, One With Fatal Outcome and Autopsy, *J Intern Coll Surgeons* 28:197, 1957.
5. Voyle, W. R., and Moretz, W. H.: Rupture of Aortic Aneurysms into Gastrointestinal Tract, *Surgery* 43:666, 1958.
6. Zak, F. G., Strauss, L., and Saphra, I.: Rupture of Diseased Large Arteries in the Course of Enterobacterial (Salmonella) Infections, *New Eng J Med* 258:824, 1958.
7. Ten Eyck, F. W., and Wellman, W. E.: Salmonellosis Associated With Abdominal Aortic Aneurysm and Edema of Lower Extremities: Case Report, *Postgrad Med* 26:334, 1959.
8. Black, P. H., Kunz, L. J., and Swartz, M. H.: Salmonellosis: A Review of Some Unusual Aspects, *New Eng J Med* 262:811, 1960.
9. Case Records of the Massachusetts General Hospital, Clinico-Pathological Conference, Case 46401, *New Eng J Med* 263:698, 1960.
10. Hyde, R. D., and Davis, P. K. B.: Infection of an Aortic Aneurysm With Salmonella Cholerae Suis, *Brit Med J* 1:30, 1962.
11. Case Records of the Massachusetts General Hospital, Clinico-Pathological Conference, Case 8, *New Eng J Med* 266:249, 1962.
12. Silberman, S., and Greenblatt, M.: Primary Mycotic Aneurysm of the Aorta: A Complication of Salmonellosis, *Angiology* 14:372, 1963.
13. Nichol, E. S., and Dobrin, M.: Gonococcus Aortitis With Multilocular Aneurysm and Congenitally Bicuspid Aortic Valve: Case Report, *Am Heart J* 12:740, 1936.
14. Stryker, W. A.: Traumatic Saccular Aneurysm of the Thoracic Aorta, *Am J Clin Path* 18:152, 1948.
15. Saphir, O., and Pooper, G. W.: Acute Suppurative Aortitis Superimposed and Syphilitic Aortitis: Report of a Case, *Arch Path* 4:543, 1927.
16. Case Report of the Massachusetts General Hospital, Clinico-Pathological Conference, Case 40331, *New Eng J Med* 251:311, 1954.
17. Crane, A. R.: Primary Multilocular Mycotic Aneurysm of the Aorta, *Arch Path* 24:634, 1937.
18. Parkhurst, G. F., and Decker, J. P.: Bacterial Aortitis and Mycotic Aneurysm of the Aorta: A Report of Twelve Cases, *Am J Path* 31:821, 1955.
19. Sommerville, R. L., Allen, E. V., and Edwards, J. E.: Bland and Infected Arteriosclerotic Abdominal Aortic Aneurysms: A Clinicopathologic Study, *Medicine* 38:207, 1959.
20. Ten Eyck, F. W., Osmundson, P. J., and Brandenburg, R. O., Edwards, J. E.: Aneurysms of the Abdominal Aorta and Fever, *Proc Staff Meet Mayo Clinic* 35:, 1960.
21. Domart, A., Labram, C., and Gregoire, J. A.: A Febrile Form of Aneurysm of the Abdominal Aorta, *Coeur Med Interne* 2:377, 1963.
22. Makins, G. H.: Specimens Showing the Effects of Gunshot Injury on the Heart and Blood Vessels, *Brit J Surg* 8:107, 1920.
23. Edwards, J. E.: An Atlas of Acquired Diseases of the Heart and Great Vessels, Philadelphia: W. B. Saunders Co., 1961, Vol. 3, p. 1033.
24. Foster, J. H., and Vetto, R. M.: Aortic Intra-Aneurysmal Abscess Caused By Sigmoid-Aortic Fistula, *Am J Surg* 104:850, 1962.
25. Garamella, J. J., Schmidt, W. R., Jensen, H. K., and Lynch, M. F.: Traumatic Aneurysms of the Thoracic Aorta: Report of Four Cases, Including One of Spontaneous Rupture Into the Esophagus, *New Eng J Med* 266:1341, 1962.

Nephrotic Syndrome in Myeloma with Amyloidosis*

THOMAS KAHN M.D.¹, JACOB CHURG M.D.², AND MARVIN
H. GOLDSTEIN M.D.³

Introduction

The nephrotic syndrome is considered to be the physiologic and biochemical consequence of marked urinary albumin loss (1, 2). Although proteinuria is common in myeloma, protein loss consists predominantly of globulins (3). Recent electron microscopic studies have revealed the frequent occurrence of glomerular basement membrane thickening in myeloma similar to that seen in many patients with nephrotic syndrome (4). Nonetheless, nephrotic syndrome associated with myeloma had not been reported prior to 1957, and only 13 cases have been recorded since then (5-10). Amyloidosis is a more frequent complication of myeloma, usually occurring in about 5 to 15 percent of cases (3, 11). The amyloid deposits in the kidney are characteristically rather scanty, however, and are usually considered to be of little clinical importance (12, 13).

It is of interest, therefore, to report two cases of myeloma with nephrotic syndrome, both of which had marked glomerular involvement with amyloid. It seems probable that, in these cases, the striking renal involvement with amyloid produced not only the nephrotic syndrome, but also significant impairment of glomerular filtration.

Case Reports

Case 1. T.R., a 52-year-old woman was seen in The Mount Sinai Hospital outpatient clinic complaining of swelling of the abdomen and lower extremities of ten months' duration, low back pain and periorbital ecchymoses of two months' duration. Her medical history included the excision of a "giant cell cyst" of the ilium two years previously. Physical examination revealed generalized abdominal distention, a palpable liver and spleen, bilateral ankle edema, periorbital ecchymoses and subconjunctival hemorrhages. Blood pressure was 120/70 mm Hg.

The hemoglobin was 11.4 gm/100 ml, white cell count 10,400 and platelet count 412,000/mm³. Urinalysis revealed a specific gravity of 1.025, 3+ protein, and many red blood cells per high power field. The blood urea nitrogen was 14 mg/100 ml, cholesterol 1040 mg/100 ml and alkaline phosphatase 60 King-Armstrong units. Serum calcium, phosphorus, and bilirubin were normal. Serum electrophoresis showed an albumin of 1.7 gm/100 ml, globulins of 5.2 gm/100 ml, with an elevated alpha-2 globulin and a spike in the region of the gamma globulin. Urine electrophoresis showed an almost identical pattern to that of the blood. Bone marrow aspiration yielded 92% plasma cells with many sheets of plasma cells.

Because of progressive weakness the patient was admitted to the hospital three months

From the Divisions of Renal Disease, Departments of Medicine and Pathology, The Mount Sinai Hospital, New York, N. Y. 10029.

* Work supported by USPHS Grants AM00918 and HTS 5-055.

¹ United States Public Health Service Post-doctoral Research Fellow.

² Associate Professor of Pathology, Mount Sinai School of Medicine, New York, N. Y.

³ Assistant Professor of Medicine, Mount Sinai School of Medicine, New York, N. Y.

later. Additional physical findings included an increase in the peripheral edema and tenderness over the lumbar vertebrae. Bence-Jones protein was present in the urine. A 24-hour urine collection contained 9.0 gm of protein of which 3.6 gm was albumin. The hemoglobin had decreased to 9.6 gm/100 ml, while the blood urea nitrogen and creatinine had risen to 34 and 2.3 mg/100 ml, respectively. A Congo red test was positive with no dye remaining in the serum 60 minutes after injection. A skeletal survey showed multiple small lucencies in the calvarium, pelvis, and femora.

The patient received supportive therapy in the hospital. However, her general condition deteriorated rapidly, associated with a falling urine output and a rise in the blood urea nitrogen to 56 mg/100 ml. She died during the fourth hospital week.

Autopsy revealed the heart, liver, and spleen to be diffusely infiltrated with amyloid. Amyloid deposits were also found in the gastrointestinal tract, tongue, and blood vessels of almost all organs. The kidneys weighed 180 grams each and had a smooth surface. All glomeruli were involved with amyloid, some being completely obliterated by it. Most glomeruli retained their lobular architecture, but the lobules were largely replaced by amyloid (Fig. 1). Amyloid was also present in the walls of blood vessels (Fig. 2). The amyloid stained faintly with Congo red and methyl violet. Only a few tubules demonstrated casts characteristic of myeloma.

Case 2. C.C., a 59-year-old woman, had noted fatigue and weight loss for three months. Three days before hospitalization she suddenly experienced left pleuritic chest pain. Her past medical history was noncontributory.

On admission the patient was in moderate respiratory distress. Dullness to percussion and bronchial breathing were noted in the left posterior lung field. The heart was slightly enlarged. The liver was palpable 4 cm below the right costal margin. A fluid wave was elicited over the abdomen and 2+ sacral and pretibial edema were noted. The blood pressure was 130/85 mm Hg and pulse was 120/minute.

The hemoglobin was 11.1 gm/100 ml and the white cell count 9800/mm³. Urinalysis

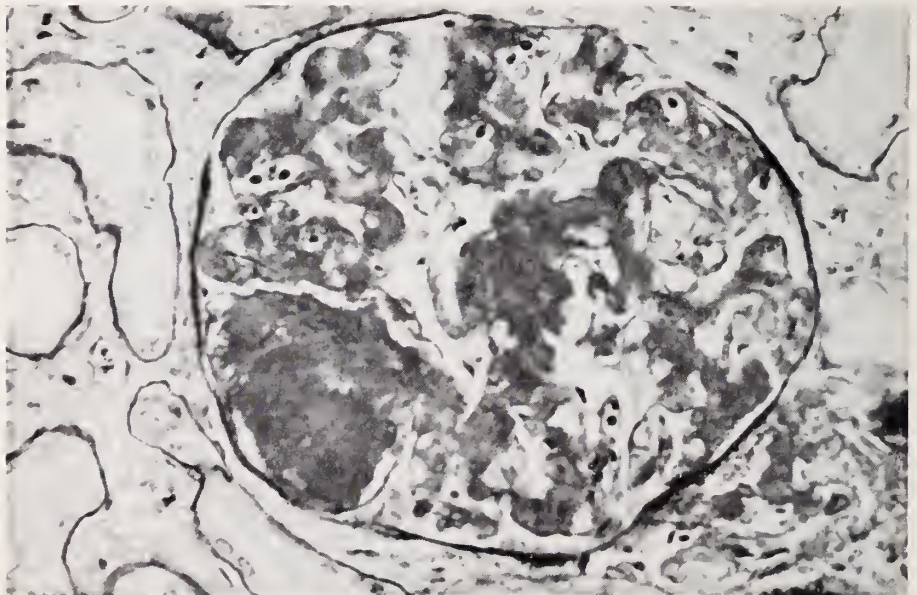


FIG. 1. Glomerulus showing extensive replacement by amyloid PAS stain. (Magnification $\times 380$)

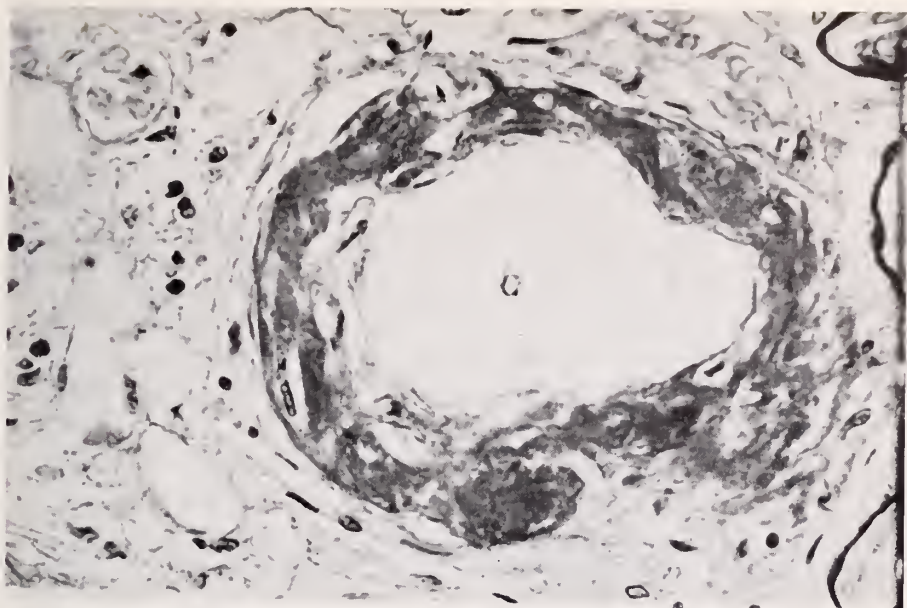


Fig. 2. Amyloid deposits in the wall of a blood vessel. PAS stain. (Magnification $\times 510$)

revealed a specific gravity of 1.010, 3+ protein, and 10 to 20 white cells per high power field. The chest x-ray showed an infiltrate in the left midlung field.

The patient was treated for an acute pulmonary embolus and improved clinically. Although all evidence of pulmonary congestion subsided, the enlarged, nontender liver and the peripheral edema persisted. The venous pressure and circulation time (arm to tongue) were normal. Further laboratory studies revealed a blood urea nitrogen of 23 mg/100 ml, albumin 1.9 gm/100 ml, globulin 3.4 gm/100 ml, cholesterol 250 mg/100 ml and calcium of 9.6 gm/100 ml. Serum electrophoresis demonstrated a spike in the gamma globulin region and an increase in the alpha-2 globulin. A 24-hour urine protein excretion was 13 gm of which 4.2 gm was albumin. Electrophoresis of the urine showed a similar pattern to that of the serum. Bence-Jones protein was present in the urine. A bone marrow aspiration demonstrated 40% plasma cells with many areas of abnormal plasma cells and some sheets of plasma cells. X-rays demonstrated a radiolucent area in the right clavicle.

During the patient's hospital course the blood urea nitrogen rose to 50 mg/100 ml and the creatinine to 2.5 mg/100 ml. Edema over the sacrum and lower extremities remained despite the use of diuretics. On the 33rd hospital day she suddenly suffered an occlusion of the left femoral artery. An embolectomy was performed, but the next day the patient went into shock and died.

Autopsy revealed evidence of an acute myocardial infarction. An adherent friable thrombus was present in the left atrium. Amyloid was heavily deposited in the parenchyma of the heart and also in the parenchyma of the liver, adrenals, spleen, and diaphragm. Evidence of a pulmonary infarction was present in the left lung. The kidneys weighed 160 gm and 200 gm each and had a smooth capsule which peeled easily. All glomeruli were involved with amyloid, some being completely replaced by deposits. In other glomeruli amyloid was present in the hilum and throughout the intercapillary space (mesangium), forming irregular streaks and small nodules (Fig. 3). The deposits stained strongly with methyl violet. Only a few casts were seen in the tubules.

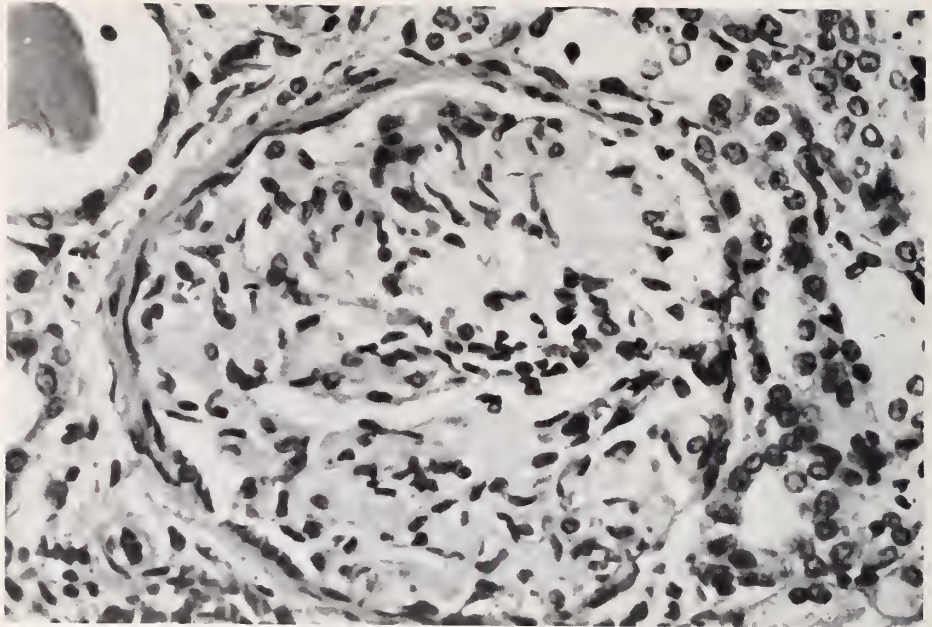


FIG. 3. Marked diffuse involvement of the glomerulus with amyloid. Hematoxylin and eosin stain. (Magnification $\times 380$)

Discussion

The amyloid associated with myeloma is usually distributed in blood vessels throughout the body and in the mesenchymal tissue primarily of the heart, gastrointestinal tract, spleen, and tongue (12). This amyloid characteristically does not stain metachromatically and has little affinity for Congo red (12). The similarity of distribution and staining characteristics between the amyloid of myeloma and that of primary amyloidosis has led to the suggestion that occult myeloma underlies most cases of primary amyloidosis (7, 12). The kidney is involved with amyloid in less than five percent of myeloma cases (3, 13), and the deposits generally are scattered throughout the cortex and medulla with relative sparing of the glomeruli (11, 12). Thus, even when amyloid is present, changes in renal function in myeloma have been attributed almost exclusively to the obstruction of tubules by proteinaceous casts rather than to any glomerular lesion (12, 13). The infrequency of the reports of a nephrotic syndrome supports this view.

Marked glomerular deposition of amyloid, however, is characteristic of the amyloidosis associated with other chronic disease states (14) and the familial amyloidoses (15, 16). When severe glomerular infiltration is present, nephrotic syndrome and azotemia leading to uremia is rather common (14, 15).

The two cases of myeloma presented here are of interest because of the widespread heavy parenchymal and blood vessel involvement of almost all organs

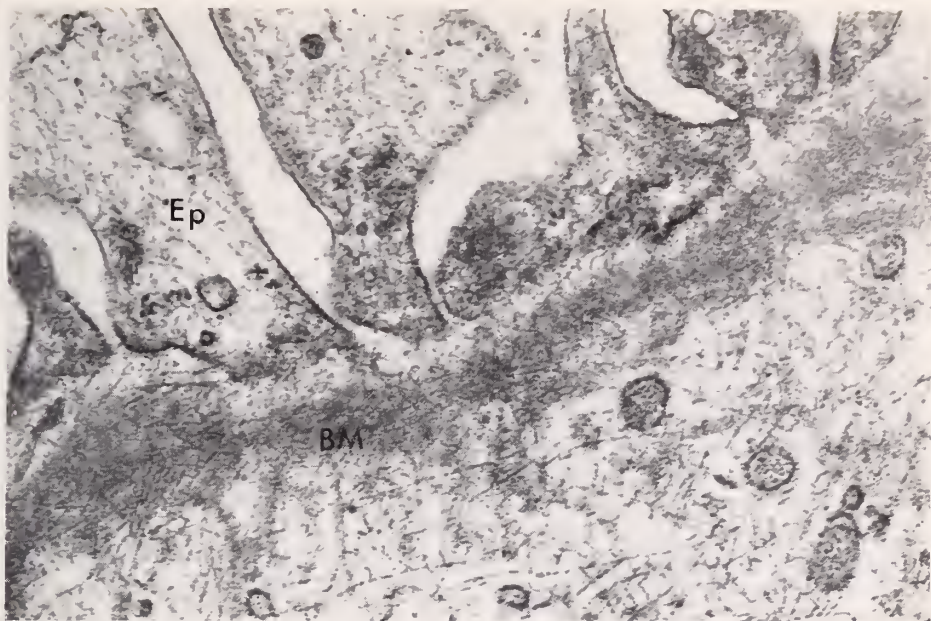


FIG. 4. Electron microscope. Portion of a glomerular capillary showing fibrils of amyloid between the endothelium and the basement membrane, within the basement membrane, and between the basement membrane and the epithelium. Epithelial foot processes are seen at the top of the picture. Ep—foot processes of the epithelial cells; BM—basement membrane. (Magnification $\times 39,000$)

of the body. Particularly noteworthy was the marked generalized glomerular involvement resulting in the complete obliteration of numerous glomeruli. It seems likely that in these two cases, in contrast to the preponderance of cases of myeloma, the amyloid deposits produced the major alterations in renal function, both in terms of increased glomerular permeability to albumin and decreased glomerular filtration resulting in azotemia. Similar widespread parenchymal and blood vessel amyloid deposition in myeloma has previously been reported only by Osserman et al in three cases, one of which had a nephrotic syndrome (9).

The mechanism whereby amyloid deposition leads to albuminuria is not clear. Studies with the electron microscope have demonstrated that the earliest glomerular deposits are found within the matrix of the intercapillary space (mesangial matrix) (17). With increasing involvement amyloid fibrils are deposited within the basement membrane (Fig. 4) and, in advanced cases, localized areas of basement membrane are almost completely replaced by amyloid (17). It is possible that these amyloid infiltrates somehow increase the permeability of the basement membrane, thus allowing the passage of almost all serum proteins into the glomerular filtrate.

Recently, three cases of nephrotic syndrome associated with myeloma without amyloid on renal biopsy have been reported (8, 10). The development of a

nephrotic syndrome in myeloma, therefore, does not necessarily indicate that the kidney is involved with amyloid. However, the present cases emphasize the point that amyloid associated with myeloma may produce severe functional pathology.

References

1. Clinard, F. P., et al: A Study of the Mechanism of Proteinuria in Patients with the Nephrotic Syndrome, *J Clin Invest* 33:621-628, 1954.
2. Churg, J., et al: Idiopathic Nephrotic Syndrome in Adults, *New Eng J Med* 272:165-174, 1965.
3. Osserman, E. F.: "Plasma Cell Dyscrasia" in *Textbook of Medicine* edited by P. B. Beeson and W. McDermott, W B Saunders, Philadelphia and London, 12th edition, 1967 Pp. 1101-1112.
4. Fisher, E., Perez-Stable, E., and Zawadzki, Z. A.: Ultrastructural Renal Changes in Multiple Myeloma with Comments Relative to the Mechanism of Proteinuria, *Lab Invest* 13:1561-1574, 1964.
5. Squire, J. R., Blainey, J. D., and Hardwicke, J.: The Nephrotic Syndrome, *Brit Med Bull* 13:43, 1957.
6. Calkins, E., and Cohen, A.: Diagnosis of Amyloidosis, *Bull Rheum Dis* 10:215-218, 1960.
7. Kyle, R., and Bayrd, E.: Primary Systemic Amyloidosis and Myeloma, *Arch Int Med* 107:344-353, 1961.
8. Larcen, A., et al: Syndrome nephrotique et maladie de Kahler, *Med Mond* 40:69-73, 1964.
9. Osserman, E. F., Takatsuki, K., and Talal, N.: The Pathogenesis of Amyloidosis in *Multiple Myeloma* edited by Miescher, P., Grune and Stratton, New York, 1964, Pp. 3-85.
10. Rosen, S., et al: Multiple Myeloma and the Nephrotic Syndrome, *Am J Clin Path* 47: 567-579, 1967.
11. Bayrd, E., and Bennet, W.: Amyloidosis Complicating Myeloma, *Med Clin N A* 34: 1151-1164, 1950.
12. Osserman, E. F.: Plasma-cell Myeloma, *New Eng J Med* 261:952, 1006-1014, 1959.
13. Bell, E. T.: Renal Lesions Associated with Multiple Myeloma, *Am J Path* 9:393-420, 1933.
14. Bell, E. T.: Amyloid Disease of the Kidneys, *Am J Path* 9:185-204, 1933.
15. Heller, H., et al: Amyloidosis in Familial-Mediterranean Fever, *Arch Int Med* 107: 539-550, 1961.
16. Muckle, T., and Wells, M.: Urticaria, Deafness, and Amyloidosis: A New Heredofamilial Syndrome, *Quart J Med* 31: 235-248, 1962.
17. Suzuki, Y., et al: The Mesangium of the Renal Glomerulus, *Am J Path* 43:555-578, 1963.

Received for publication August 19, 1968

Severe Hypoxemia in an Obese Patient with Polycythemia Vera

E. LESLIE CHUSID, M.D., ALBERT MILLER, M.D., AND
RALPH ZALUSKY, M.D.

Introduction

Oxygen saturation in polycythemia vera has been extensively discussed (1-6). It is generally stated that arterial oxygen saturation below 90 to 91 percent in a patient with polycythemia vera is uncommon and that a cause other than polycythemia vera should be sought to explain its presence. Arterial oxygen saturation averaging 85 percent was noted in an obese woman with polycythemia vera. Investigation demonstrated a severe ventilation-perfusion imbalance, most probably related to obesity.

Methods

PULMONARY FUNCTION STUDIES

Lung volume and lung dynamic studies were performed on a closed-circuit spirometer. The functional residual capacity was determined by closed-circuit helium dilution. Ventilation was measured with the subject breathing room air, 5% CO₂ in room air, 5% CO₂ and 95% oxygen, and 100% oxygen. Observations were made while the patient was resting, sitting, voluntarily hyperventilating, and exercising on a treadmill. Arterial blood was analyzed by the Van-Slyke manometric method, by oximetry, and by direct electrode techniques. Expired gases were analyzed in a micro-Scholander apparatus, and diffusion was studied by the single breath carbon monoxide method.

HEMATOLOGIC STUDIES

Peripheral blood counts were performed by routine methods. Plasma and red blood cell volumes were determined with I¹²⁵-labeled human serum albumin and Cr⁵¹-labeled autologous cells; values were related to the patient's surface area rather than weight because of her obesity (7). Plasma erythropoietin was assayed in the hypertransfused mouse (8), normal values falling below 0.3% Fe⁵⁹ red blood cell uptake in 48 hours.

Case Report

A 56-year-old white, obese woman was hospitalized in 1958 because of thrombophlebitis and probable pulmonary infarction. Routine hematologic

From the Department of Medicine, The Mount Sinai Hospital-City Hospital Center at Elmhurst, and the Department of Hematology, The Mount Sinai Hospital, New York, N. Y.

This study was supported in part by Grant CA 04457, the National Cancer Institute, the Sophie Abramson Silber Memorial Grant of the American Cancer Society, and the Albert A. List, Frederick Machlin and Anna Ruth Lowenberg Funds.

Reprints: E. Leslie Chusid, M.D., Department of Medicine, The Mount Sinai Hospital Services-City Hospital Center at Elmhurst, 79-01 Broadway, Elmhurst, N. Y. 11373.

studies were normal. Slight cardiomegaly was seen on x-ray and right axis deviation was noted on her electrocardiogram. She improved with bed rest and short-term anticoagulant therapy, and remained well for the next four years. She then noted symptoms of full-headedness and easy fatigability. Her physician found an elevated hematocrit and over the ensuing two years removed approximately ten units of blood.

When first seen by us in October 1964, physical examination revealed an obese woman who weighed 112 kg and was 168 cm in height. Vital signs were normal. She was plethoric with cyanosis of the lips and nail beds. The conjunctivae were suffused, minimal cardiomegaly with an accentuated second pulmonic sound was present, and the spleen extended 6 cm below the left costal margin. There was no evidence of congestive failure. Superficial varicosities were present in both legs. Pelvic examination was normal.

Table I shows the hematologic findings. Blood chemistries were normal other than for uric acid, which was 11.5 mg/100 ml. Slight increase in pulmonary vascular markings and mild cardiomegaly were seen on the chest film. An intravenous pyelogram showed ptosis of the right kidney, but no other abnormalities. The electrocardiogram continued to show right axis deviation with occasional extrasystoles.

In February 1965, the patient was started on Myleran®, 8 mg daily for one week; the dose was gradually reduced to 2 mg three times a week over the course of five months. The white blood cell and platelet counts remained normal following cessation of therapy. Periodic phlebotomies have been necessary to maintain a hematocrit at about fifty percent. The hematologic data are summarized in Table I.

TABLE I
Hematologic Data

	Results	Normal Values
Hemoglobin (gm/100 ml)*	16.4	14.0 \pm 2.0
Hematocrit (%)	56	42.0 \pm 5.0
Erythrocytes (10^6 /mm ³)*	6.26	4.8 \pm 0.6
Reticulocytes (%)	3.1	0.5-1.5
White Blood Cells (per mm ³)*	14,000	5,000-10,000
Platelets (per mm ³)*	600,000	150,000-450,000
Serum Iron (μ g/100 ml)*	20	50-130
TIBC (μ g/100 ml)*	403	150-300
Whole Blood Volume† (ml/M ²)	2789	2400 \pm 324
Red Cell Mass† (ml/M ²)	1329	930 \pm 182
Plasma Volume† (ml/M ²)	1460	1410 \pm 193
Red Cell Survival (T/2 Cr ⁵¹ , days)†	27	27-32
Leukocyte Alkaline Phosphatase (score)*	328	25-100
Plasma Erythropoietin Level (% Fe ⁵⁹ uptake)†	0.18‡	<0.30

* October, 1964, receiving periodic phlebotomies.

† November, 1966, receiving periodic phlebotomies and chemotherapy.

‡ Average of five mice.

TABLE II
Spirometric, Ventilation, and Diffusion Studies

Study	1964	1966
Vital Capacity (ml) . . .	2850 (91%)†	2500 (80%)
Residual Volume (ml) . .	1425 (80%)	1350 (76%)
Total Lung Capacity (ml)	4275 (87%)	3960 (80%)
RV, TLC	33%	34%
Forced Vital Capacity (ml) . .	2850	2500
Forced Expiratory Volume (1 sec)	71%	78%
Maximal Expiratory Flow Rate (liters/min)* . .	222	223
Maximal Voluntary Ventilation (liters/min) . .	90 (106%)	84 (100%)
Minute Ventilation (liters/min/BSA) Room Air† . .	5.4	5.8
Minute Ventilation (liters/min/BSA) 5% CO ₂ . .		11.9
Diffusion (DCO _{SB})		17.4§ (106%)
Alveolar-Arterial Gradient for pO ₂ , Room Air (mm Hg)*	56	31

* Normal in our laboratory = 200 L/min.

† Normal = 3-4 L/min/BSA.

‡ % predicted.

§ Average of 3 determinations.

|| Reference 9.

• Normal = <15 mm Hg.

In January 1967, the patient was again hospitalized for thrombophlebitis and myocardial ischemia, and was again suspected of having pulmonary embolism. She was placed on anticoagulant therapy and was discharged improved.

Pulmonary function studies were performed several times over the course of three years. Lung volumes and dynamics were normal. Diffusing capacity for carbon monoxide (DLCO_{SB}) was normal. Moderate hyperventilation was always present. The alveolar-arterial gradient for pO₂ at room air was significantly elevated on two occasions, consistent with venous admixture effect.

Arterial oxygen tension and saturation were always significantly reduced, and respiratory alkalosis was often manifest. Oxygen values rose with sitting and frequently became normal with voluntary hyperventilation.

While breathing 100% oxygen on two occasions the arterial pO₂ was only 192 mm Hg and 300 mm Hg, respectively, but rose strikingly with either voluntary or CO₂-induced hyperventilation.

Results of pulmonary function and arterial blood gas studies are shown in Tables II and III.

Discussion

Arterial oxygen saturation has long been used to separate most cases of polycythemia vera from the most common form of secondary erythrocytosis, that due to hypoxemia. The patient described here satisfied these criteria for the diagnosis of polycythemia vera: (1) increase in all the formed elements

TABLE III
Arterial Studies

	12/10/64	1/26/65	6/8/65	5/12/66	12/13/66
Room Air Recumbent	*SaO ₂ = 86%	SaO ₂ = 79% pCO ₂ = 38 pH = 7.40	SaO ₂ = 84% pCO ₂ = 34 pH = 7.41	SaO ₂ = 92% pCO ₂ = 30 pH = 7.45 pO ₂ = 78	SaO ₂ = 87% pCO ₂ = 35 pH = 7.48 pO ₂ = 49
Sitting			SaO ₂ = 89% pCO ₂ = 34 pH = 7.40		
Hyperventilation		SaO ₂ = 91% pCO ₂ = 34 pH = 7.42	SaO ₂ = 96% pCO ₂ = 23 pH = 7.46		SaO ₂ = 98% pCO ₂ = 20 pO ₂ = 102 pH = 7.60
100% Oxygen Recumbent				SaO ₂ = 100% pCO ₂ = 24 pO ₂ = 194 pH = 7.48	SaO ₂ = >100% pCO ₂ = 32 pO ₂ = 300 pH = 7.44
Hyperventilation					SaO ₂ = >100% pCO ₂ = 33 pO ₂ = 590 pH = 7.47
5% CO ₂ and 95% O ₂ Recumbent					SaO ₂ = >100% pCO ₂ = 50 pO ₂ = 570 pH = 7.34

* SaO₂ = Arterial Oxygen Saturation.

of the blood; (2) elevated red blood cell mass; (3) high serum uric acid; (4) elevated leukocyte alkaline phosphatase, (5) splenomegaly, and (6) no elevation of plasma erythropoietin. Her arterial oxygen saturation and tension were much lower than levels usually reported in this disease.

Results of pulmonary function testing eliminated alveolar hypoventilation and diffusion impairment as causes of the hypoxemia. Ventilation-perfusion imbalance with venous admixture effect was evidenced by increased alveolar-arterial gradient for pO₂ at room air, and the inadequate rise in pO₂ on quiet breathing of 100% O₂. Oxygen saturation increased in the sitting position, as compared with recumbency, and often became normal with voluntary hyperventilation. Arterial pO₂ rose much more with voluntary hyperventilation of 100% oxygen or with breathing a 5% CO₂-95% O₂ mixture, than with quiet breathing of 100% O₂.

These findings suggest obesity, with areas of unventilated but perfused alveoli during quiet breathing, as the reason for ventilation-perfusion imbalance. The improvement in oxygenation obtained with change in position and hyperventilation resulted from improvement of ventilation in underventi-

lated alveoli. Although inhalation of 100% oxygen has been widely used to detect venous admixture (10), comparing the pO_2 achieved during hyperventilation with that achieved by quiet breathing of oxygen has not been emphasized in the literature.

That pulmonary embolism may have played a role in the venous admixture cannot be discounted. However, pulmonary embolization would not explain the effects of posture and hyperventilation so well as obesity. Any role of the polycythemia itself in producing the venous admixture and hypoxemia cannot be evaluated from the studies performed.

The usual reasons for the mild unsaturation not infrequently found in polycythemia vera have been described as: 1. Lung restriction causing alveolar hypoventilation (5); 2. thrombosis of the respiratory center causing hypoventilation (2, 5); or 3. thrombosis in the pulmonary capillary bed and increased viscosity causing impaired diffusion (2, 3, 5). None of these mechanisms were demonstrable in the patient described here. Although altered ventilation-perfusion balance has been suggested in polycythemia vera, it has not been confirmed (2, 3, 5, 6).

Summary

Ventilation-perfusion relationships were investigated in an obese woman with the unusual combination of polycythemia vera and moderately severe arterial oxygen unsaturation (*ca.* 85%). The hypoxemia was found to be secondary to venous admixture, was corrected by hyperventilation, and was best explained by her obesity.

References

1. Wasserman, L. R., Dobson, R. L., and Lawrence, J. H.: Blood Oxygen Studies in Patients with Polycythemia and in Normal Subjects, *J Clin Invest* 28:60, 1949.
2. Lertzman, M., et al: Hypoxia in Polycythemia Vera, *Ann Int Med* 60:409, 1964.
3. Murray, J. F.: Arterial Studies in Primary and Secondary Polycythemic Disorders, *Am Rev Resp Dis* 92:435, 1965.
4. Murray, J. F.: Classification of Polycythemic Disorders, *Ann Int Med* 64:892, 1966.
5. Newman, W., Feltman, J., and Devlin, B.: Pulmonary Function Studies in Polycythemia Vera, *Am J Med* 11:706, 1951.
6. Bader, R., Bader, M., and Duberstein, J. L.: Polycythemia Vera and Arterial Oxygen Saturation, *Am J Med* 34:435, 1963.
7. Karlson, K. E., and Suen, L. Y.: Simultaneous Determination of Red Cell Mass and Plasma Volume with Cr^{51} and I^{131} Using a Pulse Height Analyzer, *Ann Surg* 158: 309, 1963.
8. Rosse, W. F., Waldmann, T. A., and Houston, D. E.: Erythropoietin Assays Using Iron⁵⁹ Incorporation into Blood and Spleen of the Polycythemic Mouse, *Proc Soc Exp Biol and Med* 109: 836, 1962.
9. Bates, D. V., and Christie, R. V.: *Respiratory Function in Disease*, 1964, p. 104. Philadelphia: W. B. Saunders Company.
10. Comroe, J. H., et al: *The Lung. Clinical Physiology and Pulmonary Function Tests*, Ed 2 Chicago: Yearbook Medical Publishers, 1962, p. 103.

Received for publication June 14, 1968

Reversible Granulocytopenia in a Patient with Polycythemia Vera Taking Nitrofurantoin

Report of a Case

STUART B. LEVY, M.D., BURT MEYERS, M.D., AND
HAROLD MELLIN, M.D.

Nitrofurantoin (Furadantin®) is a commonly used urinary tract antiseptic. Although adverse reactions have been reported in patients treated with this drug (1-8), it is regarded as a relatively safe antibiotic. The drug is usually not given for more than a two-week period (9), but recent advertising has encouraged its long-term use in chronic urinary problems. We report an instance of reversible granulocytopenia in a patient with polycythemia vera who was taking the drug for thirty-four days.

Case Report

H.P., a 52-year-old white police officer, was admitted for the first time to The Mount Sinai Hospital for increasing weakness, pain in the lower extremities, urinary retention, and fecal incontinence of one month's duration.

Four weeks prior to admission the patient awoke with pain and weakness in his legs progressing, over the next two days, to paresis of his lower extremities. At this time the sudden development of inability to void and fecal incontinence prompted his admission to a local hospital for treatment. During this admission a high hematocrit (87%) was found as well as benign prostatic hypertrophy. No corrective surgery was attempted because of his hematologic condition. A Foley catheter was inserted and a phlebotomy was performed yielding eleven units of blood. He was then transferred to The Mount Sinai Hospital for further hematologic and neurologic evaluation.

The patient's initial blood pressure was 140/90, pulse was regular at 88/min, respirations 24/min and a temperature of 99°F. He was somewhat cachectic with a ruddy face and neck. Funduscopic examination revealed only engorged vessels. Heart and lungs were unremarkable. The liver was enlarged; the edge was palpated one centimeter below the right costal margin. The spleen was felt four centimeters below the left costal edge. A Foley catheter was in place. The anal sphincter was relaxed; a slightly enlarged nontender prostate was palpated. Pulses were easily palpable and equal in all extremities.

The patient was oriented to time, place, and person. Cranial nerve func-

From the Departments of Medicine and Hematology, The Mount Sinai Hospital, New York, N. Y.

Reprints: Dr. Stuart Levy, National Institute of Arthritis and Metabolic Diseases, NIH, Building 4, Bethesda, Maryland 20014.

This study was supported in part by USPHS grants CA-04457 and CA-05126 from the National Cancer Institute and grant T-360A, The Sophie Abranson Silber Memorial Grant for Cancer Research from the American Cancer Society, and the Albert A. List, Frederick Machlin, and Anna Ruth Lowenberg Research Funds.

tion was intact. Sensory abnormalities consisted of frequent errors in position sensation in both legs, especially the left, and decreased pinprick sensation in the left leg. No sensory level could be found. The deep tendon reflexes were absent in the lower extremities. No abnormal reflexes were elicited. Weakness and some atrophy was obvious in the left calf muscles.

Initial laboratory studies revealed a hemoglobin of 18.1 gm%, hematocrit of 60%, red blood cell count 5.9 million and white blood cell count of 12,450 (85 segs, 2 bands, 9 lymphs, 3 eos, 1 mono). The platelet count was 294,000, reticulocytes 3% and erythrocyte sedimentation rate of 0. Bone marrow aspiration showed normocellularity with a marked increase in the erythroid elements. The myeloid: erythroid ratio was 1:1. Fifty percent of the neutrophils were bands and polys. Bone marrow biopsy showed no evidence of fibrosis. Urinalysis showed clear, acid urine with a specific gravity of 1.005 and 5-10 WBC per high power field. Thyroid studies, EEG, ECG, chest x-ray, arterial pO₂ values, urine porphobilinogens, serum iron, B₁₂ and folic acid determinations were all normal. Serum uric acid was 5.5 mg% with an increased urinary uric acid excretion (920 mg/24 hrs.); the urinary creatinine excretion was 882 mg/24 hrs. The leukocyte alkaline phosphatase level was elevated at 234. Subsequent blood volume studies when his hematocrit was 57% showed an increased red cell mass (44.4 ml/kg). The diagnosis of polycythemia vera was made.

The patient was thought to have a space-occupying cauda equina lesion, but a normal myelogram and two lumbar punctures with normal manometries and chemistries failed to substantiate this suspicion. Cystometries showed a neurogenic bladder, and a voiding intravenous pyelogram demonstrated some prostatic calculi and hypertrophy with no evidence of renal cysts, tumor, or hydronephrosis. No single vascular thrombosis could explain the diffuse neuropathy. And, in view of the negative findings on myelography and the absence of long tract signs, the patient was thought to have a nonspecific polyneuropathy. Soon after admission a phlebotomy yielded four units of blood, thus reducing his hematocrit to 46% where it remained throughout hospitalization.

Gradually over the next month, with the aid of physical therapy his motor strength improved and he was able to walk with a cane. A suprapubic cystostomy was performed without difficulty. He sustained two attacks of thrombophlebitis, one of which led to a pulmonary embolus for which he was treated with heparin and then sodium warfarin (Coumadin®).

Because of a persistent urinary tract infection and low grade fever the patient was treated with several antibiotics. These were changed as different sensitivities were found: sulfisoxazole (Gantrisin®) for five days; nalidixic acid (Neg Gram®) for seven days; and finally Furadantin® for thirty-four days (400 mg/day). The only other medication was phenobarbital which he had been taking since admission. Routine blood counts were taken weekly. On the thirty-fourth day of Furadantin® therapy a leukopenia with a relative eosinophilia was noted (1830: 20 seg, 1 band, 53 lymphs, 18 eos, 3 basos and 5 monos). His hematocrit remained at 45% and the platelet count at 320,000. A repeat bone marrow now showed diminished cellularity with an arrest in the

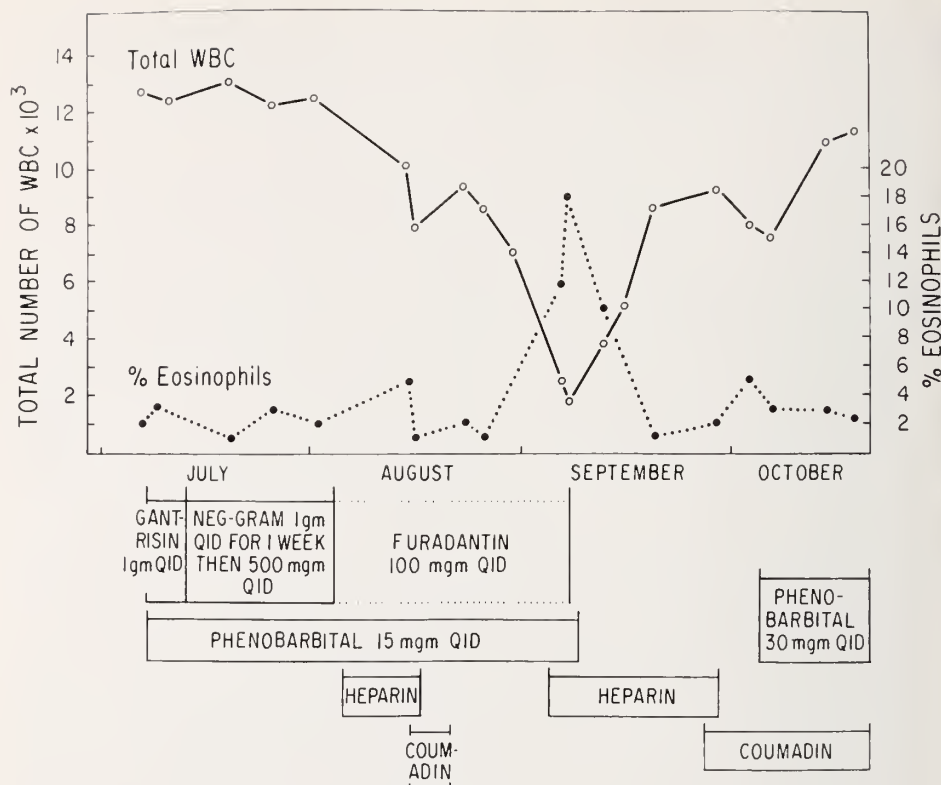


FIG. 1. Medication vs. peripheral white blood cell counts of patient during hospitalization.

neutrophilic series at the metamyelocyte stage. Only 10% of the neutrophils were bands and polys; the M:E ratio remained at 1:1. An increase in eosinophilic granulocytes was noted. Except for some left calf pain from a recent thrombophlebitis, the patient was asymptomatic. All medication was stopped. He was maintained on heparin, however; he had not received Coumadin® for three weeks.

Within five days following the termination of Furadantin® (see figure) the white blood cell count had risen to 3850 and within twelve days to 8685 (70 segs, 7 bands, 13 lymphs, 1 eos, 1 baso, 8 monos). A repeat bone marrow taken twelve days after stopping Furadantin® now showed return to normocellularity. Thirty percent of the neutrophils were now bands and polys; the M:E ratio was 2:1.

Subsequently the patient was challenged with both Coumadin® and Pheno-barbital maintained for at least a three-week period with no fall in the white blood cell count. He was given one dose (100 mg) of Furadantin® with no ill effect. Further doses of the drug were felt unwise in view of the retesting experiences of other investigators (2, 5). Because of the report of sensitivity

to Furadantin® in individuals deficient in glucose-6-phosphate dehydrogenase (1), this enzyme was studied in this patient and found not to be diminished (2380 units, normal value, 1700).

Comment

To our knowledge there is only one case report in the literature of granulocytopenia occurring in a patient receiving Furadantin® (7). This patient had systemic lupus erythematosus and had also been taking the drug for more than two weeks. In the present case, the unusual development of leukopenia in untreated polycythemia was observed. Serial blood counts, bone marrows, and the patient's response to stopping the drug suggest that Furadantin® was the causative agent. Whether this reaction is other than idiosyncratic in this patient with known hematologic disease is unknown. But the clinician should be aware of this possible complication of long-term Furadantin® therapy.

Summary

A patient with untreated polycythemia vera became granulocytopenic with bone marrow arrest at the metamyelocytic stage after thirty-four days of nitrofurantoin therapy for urinary tract infection. Elimination of the drug resulted in a prompt return to his previous bone marrow and peripheral blood condition. This report suggests that long-term therapy with nitrofurantoin may be potentially harmful to bone marrow.

References

1. Kimbro, E. L. Jr., Sachs, M. V., and Torbert, J. V.: Mechanism of the Hemolytic Anemia Induced by Nitrofurantoin (Furadantin®). Further Observations on the Incidence and Significance of "Primaquine-sensitive" Red Cells, *Bull Johns Hopkins Hosp* 101:245-257, Nov., 1957.
2. Fisk, A. A.: Anaphylactoid Reaction to Nitrofurantoin, *New Eng J Med* 256:1054, May, 1957.
3. Martin, W. J., Corbin, K. B., and Utz, D. C.: Paresthesia during Treatment with Nitrofurantoin: Report of a Case, *Proc Staff Meeting Mayo Clinic* 37:288-292, May, 1962.
4. Ellis, F. G., and Lond, M. S.: Acute Polyneuritis after Nitrofurantoin Therapy, *Lancet* 2:1136-1138, Dec., 1962.
5. Israel, H. L., and Diamond, P. D.: Recurrent Pulmonary Infiltration and Pleural Effusion due to Nitrofurantoin Sensitivity, *New Eng J Med* 266:1024-1026, May, 1962.
6. DeVeber, L. L., and Valentine, G. H.: Nitrofurantoin and Megaloblastic Anemia, *Lancet* 2:697-698, Sept., 1964.
7. McDuffie, F. C.: Bone Marrow Depression after Drug Therapy in Patients with Systemic Lupus Erythematosus, *Ann Rheum Dis* 24:289-292, May, 1965.
8. Sollacio, P. A., Ribaldo, C. A., and Grace, W. T.: Subacute Pulmonary Infiltration due to Nitrofurantoin, *Ann Int Med* 65:1284-1286, Dec., 1966.
9. Esplin, D. W.: Antiseptics and Disinfectants; Fungicides; Ectoparasiticides" in Goodman, L. S. and Gilman, A. *The Pharmacological Basis of Therapeutics*, 3 Ed, New York: Macmillan Co., 1965, p. 1044.

Received for publication June 2, 1968

Peripelvic Urine Granuloma

Case Report

STEVEN ALEXANDER, M.D.*, RUTH SCHWARZ, M.D., AND
HAROLD J. SOBEL, M.D.

The recent urological and radiological literature contain a few case reports describing the extravasation of urine into the peripelvic tissues (1, 2). This is found to occur during episodes of acute ureteral obstruction which produces a rapid increase in the renal pelvic pressure. Although the clinical sequelae of urinary extravasation are presumed to be almost nil, there are now reports which describe significant complications such as perinephric abscess and peripelvic urine granulomas (3, 4). The following report is of a case which required a renal exploration for the delineation of a flank mass.

Case Report

A 38-year-old Puerto Rican woman was examined in the emergency room because of severe right flank tenderness and nausea of several hours' duration. There was no prior history of urolithiasis.

The patient was in acute distress and her temperature was 101°F. There was exquisite tenderness in the right flank and right upper quadrant of the abdomen, and a mass was palpable in this area. The significant laboratory data included microscopic hematuria, anemia, and a peripheral leukocytosis with a marked shift to the left.

Intravenous urography demonstrated a peripelvic extravasation of contrast media around the right kidney (Fig. 1). Right retrograde pyelography confirmed the presence of the extravasate with marked distortion of the lower pole calyx (Fig. 2). A ureteral calculus was not demonstrated.

Nephrotomography revealed obliteration of the right psoas shadow and marked distortion and displacement of the calyces of the right kidney suggestive of a mass in the lower pole (Fig. 3).

Aortography and selective right renal arteriography showed no evidence of a neoplasm (Fig. 4). A collection of dye was noted in the parenchyma of the right kidney just above the inferior minor calyx.

During the clinical evaluation of the patient, the mass in the right upper abdomen diminished in size. However, the patient continued to have pain and a septic course. Therefore, right renal exploration was carried out through a flank incision.

The right kidney was enlarged, and the lower pole was thickened and indurated. The indurated tissue extended to the renal pelvis and vessels, and down the ureter. Furthermore, it was adherent to the posterior muscles. A

From the Departments of Urology and Pathology and The Max Wachstein Research Laboratories, Beth Israel Hospital, Passaic, New Jersey.

This study was supported by research grant HE-05950 of the National Heart Institute.

FIG. 1. Intravenous pyelogram demonstrating peripelvic extravasation of contrast media around the right kidney with distortion of the lower calyx.



FIG. 2. Right retrograde pyelogram confirming the extravasation and calyceal distortion.



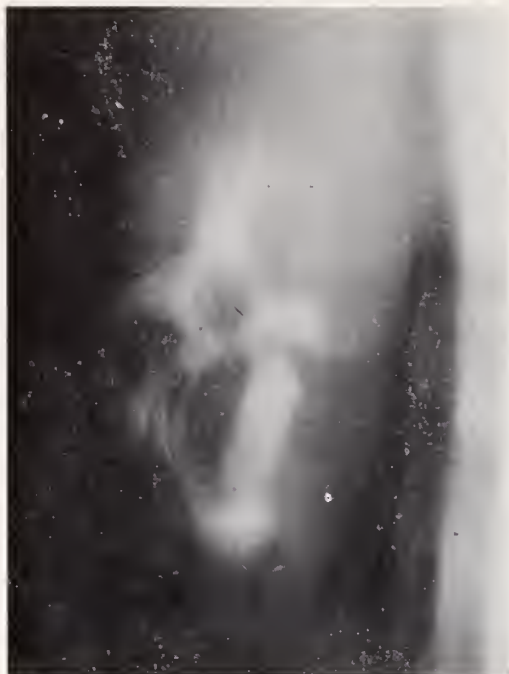


FIG. 3. Nephrotomogram demonstrating marked distortion and displacement of the calyces suggestive of a mass in the lower pole.



FIG. 4. Right selective renal arteriogram showing no evidence of neoplasm.

frozen section of this tissue demonstrated only acute and chronic nonspecific inflammation. A right nephrectomy with excision of the indurated peripelvic mass was performed with great difficulty due to the extensive inflammatory reaction.

A right pneumothorax developed in the patient which required needle aspiration. She then had a satisfactory postoperative recovery without fever. She has been observed for a period of five months following her discharge from the hospital. There is no pain or fever. The hemoglobin level has been stable, and she feels well.

Pathology

The surgical specimen consisted of a large kidney weighing 190 grams, with a moderately dilated pelvis. A mass measuring $2\frac{1}{2}$ cm in diameter was noted in the lower pole of the kidney. On section this was found to be a markedly dilated calyx containing hemorrhagic material and with focal destruction of its wall (Figs. 5, 6). The fibro-fatty tissue received for frozen section, and the periureteral connective tissue and fat revealed firm, nodular, and opaque foci. Microscopic examination revealed fresh blood in the dilated calyx with loss of mucosa, thinning and destruction of its muscle coat and underlying fibrosis with mild chronic inflammation (Fig. 6). The nodular foci on section consisted of a pink hyaline material, resembling amyloid or renal tubular casts, separating strands of connective tissue (Fig. 7). Foci of hemorrhage and a few lymphocytes and lipophages were noted in the adjacent scarred area. The pink deposits stained strongly with the periodic acid-Schiff procedure as do tubular casts. Stains for amyloid were negative.

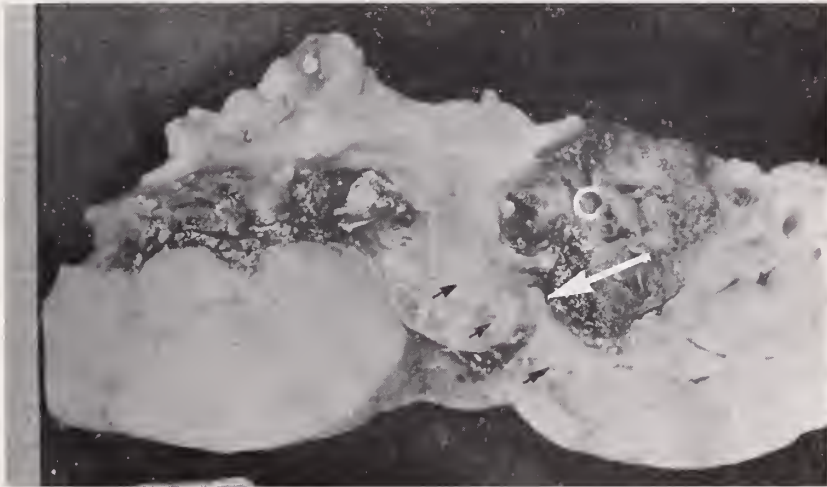


FIG. 5. Section through the lower pole of the right kidney bisecting the inferior calyx (c) which is markedly dilated and contains hemorrhagic material. A rent is noted in the wall of the calyx at large arrow. The underlying pericalyceal connective tissue and fat reveal firm, nodular, and opaque foci (small arrows).

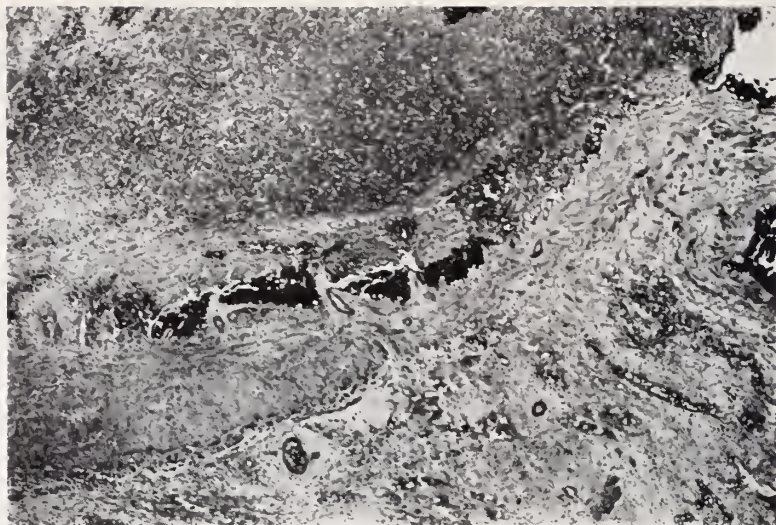


FIG. 6. Microscopic section of the calyx seen in Fig. 5. Recent hemorrhage is noted in its lumen with loss of mucosa, thinning and destruction of its muscle coat, and underlying fibrosis with mild chronic inflammation. Hematoxylin and eosin; $\times 32$.



FIG. 7. Microscopic section of a nodular and opaque focus seen in Fig. 5. Note hyaline material separating fibrous strands with many erythrocytes and few lymphocytes and lipophages in adjacent scarred area. Hematoxylin and eosin; $\times 187$.

Discussion

Peripelvic extravasation of urine has generally been described with associated renal colic (5). The entity has been recognized more frequently in recent years since excretory urography is now being carried out during or immediately following an episode of renal colic (6).

The extravasate is produced by a rapid rise in the intrapelvic pressure caused by an acute ureteral obstruction (7). The increased intrapelvic pressure produces a tear in the fornix of a calyx. Urine can then travel into the sinus of the kidney along the infundibulum of a calyx (3). It may readily penetrate a porous leaf of the renal capsule to escape around the kidney and pelvis.

Hinman, Jr. demonstrated that a potential route exists for the spread of substances between the fornix and peripelvic tissues (8). He administered an azo dye (Pyridium) to animals and patients with extravasation and observed that the orange-colored urine travelled through the hilus of the kidney into the perirenal fat within Gerota's fascia. He concluded that this phenomenon represented an extreme form of pyelosinus backflow, and is basically a physiological occurrence in the presence of an acute ureteral obstruction.

It is generally felt that surgical intervention or cystoscopy with the passage of ureteral catheters is not indicated (9). The extravasate is usually reabsorbed, and subsequent urograms are generally normal.

There are, however, reports of serious complications associated with urinary extravasation. Harrow described a case in which spontaneous urinary extravasation associated with renal colic initiated a perinephric abscess (3). Incision and drainage of abscess was required. This author also feels that extravasation may sometimes produce a dense fibrotic reaction around the renal pelvis and upper ureter with subsequent urinary obstruction. He suggests that peripelvic extravasation accounts for some cases of fibrolipomatosis of the renal sinus, and occasionally, strictures of the upper ureter and calyceal infundibuli.

Hamperl and Dallenbach described urinary extravasation into renal sinus tissues with fibrosis (10). The resulting cicatrix may compress and narrow the calyx, pelvis, or ureter, and may sometimes simulate a tumor.

Pawlowski termed this entity "peripelvic urine granuloma" (4). He described six cases (two in detail) to support the theory that the deposits result from precipitated, probably altered, extravasated urine. As evidence, it was noted that these deposits are related to calculous disease, and ruptures or scars are frequently noted in the adjacent calyces. They resemble and stain identically with tubular casts strongly suggesting that these deposits are urinary precipitates.

Summary

A case of urinary extravasation producing a flank mass with sepsis mimicking a perinephric abscess is reported. The extravasation was demonstrated by x-ray, and confirmed by tissue examination.

Serious complications associated with spontaneous peripelvic extravasation have been reported infrequently. The pathogenesis of the extravasation is discussed.

Acknowledgment

The authors are indebted to Mr. Eugene Marquet for technical and photographic assistance.

References

1. Braun, W. T.: Peripelvic Extravasation during Intravenous Urography, *Amer J Roentgenology, Radium Therapy, and Nuclear Medicine* 98:41, 1966.
2. Ginsberg, S. A.: Spontaneous Urinary Extravasation in Association with Renal Colic, *J Urol* 94:192, 1965.
3. Harrow, B. R.: Spontaneous Urinary Extravasation Associated with Renal Colic Causing a Perinephric Abscess, *Amer J Roentgenology, Radium Therapy, and Nuclear Medicine* 98:47, 1966.
4. Pawlowski, J. M.: Peripelvic Urine Granuloma, *Amer J Clin Path* 34:64, 1960.
5. Harrow, B. R., and Sloane, J. A.: Pyelorenal Extravasation during Excretory Urography, *J Urol* 85:995, 1961.
6. Schwartz, A., Caine, M., Hermann, G., and Bitterman, W.: Spontaneous Renal Extravasation during Intravenous Urography, *Amer J Roentgenology Radium Therapy, and Nuclear Medicine* 98:27, 1966.
7. Rabinowitz, J. G., Keller, R. J., and Wolf, B. S.: Benign Peripelvic Extravasation Associated with Renal Colic, *Radiology* 86:220, 1966.
8. Hinman, F., Jr.: Peripelvic Extravasation during Intravenous Urography; Evidence for an Additional Route for Backflow after Ureteral Obstruction, *J Urol* 85:385, 1961.
9. Forsythe, W. F., Huffman, W. L., Schildt, P. J., and Persky, L.: Spontaneous Extravasation during Urography, *J Urol* 80:393, 1958.
10. Hamperl, H., and Dallenbach, F. D.: The Extravasation and Precipitation of Urine in the Hilus of the Kidney, *J Mt Sinai Hosp* 24:929, 1957.

Received for publication July 22, 1968

Neurologic Manifestations of Neuroblastoma

JACK N. ALPERT, M.D.¹, AND ROBERT MONES, M.D.²

Introduction

Neuroblastoma is one of the common malignant neoplasms of childhood comprising ten percent of malignancies in one reported series of over 400 cases (1). There have been few cases in adults. The neoplasm usually originates in the sympathetic ganglia or adrenal medulla and rarely arises in the parenchyma of the cerebrum (2-5). The tumor cells may evolve either directly from immature neural crest cells developing into cells of the sympathetic system or from mature cells which undergo malignant degeneration (6).

The clinical manifestations of neuroblastoma include those resulting from local invasion or from metastases via the lymphatic or hematogenous systems. Both processes often produce either early or late neurologic signs. Previous clinical studies of neuroblastoma (1, 6-10) focused primarily on systemic manifestations and dealt only incidentally with the neurologic complications. However, there are studies confined to a description of metastatic disease to the spinal cord which deal with the neurologic defects in detail (11-14). Our study is an analysis of all the sites of neurologic involvement and the resultant signs, symptoms, and clinical course of patients with neuroblastoma.

Case Reports

The records of patients with known nervous system involvement by neuroblastoma were reviewed. These patients were seen at Memorial Hospital over a 10-year period. A histologic diagnosis of neuroblastoma was made either during surgery or by biopsy in every case. Not all of the cases have been thoroughly evaluated clinically but all patients have had unequivocal evidence of disease of the nervous system with adequate information for at least gross anatomic localization. Several cases have been selected as providing characteristic or interesting clinical pictures.

Case 1. A five-year-old girl was admitted to Memorial Hospital for the first time with a one-week history of listlessness and anorexia.

Physical examination revealed an abdominal mass and no expansion of the right side of the chest. Chest film showed opacification of the right lung and a density in the left lung. Thoracentesis revealed tumor cells with the histologic characteristics of neuroblastoma. Radiotherapy to the chest was given.

Second Admission: Neurologic symptoms did not develop until approximately seven months later when the patient was admitted with a three-week history of headache and vomiting.

Examination revealed bilateral papilledema with no other neurologic signs. Lumbar

From the Department of Neurology, The Mount Sinai Hospital and the Department of Neuropsychiatry, Memorial Hospital, New York City.

¹Resident in Neurology, The Mount Sinai Hospital, New York, N. Y.

²Assistant Clinical Professor of Neurology, Mount Sinai School of Medicine, New York, N. Y.

puncture showed an opening pressure of 450 mm of water, a protein of 18 mg%, one mononuclear cell, and a negative culture. Skull films disclosed separation of the sutures and a right carotid angiogram demonstrated an obstruction of the sagittal sinus. The patient was treated with radiotherapy to the brain.

Subsequent neurologic examinations revealed, in addition to bilateral papilledema, weakness of dorsi and plantar flexion at the right ankle, an absent right ankle jerk, a positive straight leg raising test on the right side, and increased warmth of the right foot. These signs suggested involvement of the lumbosacral plexus and radiotherapy was begun in this area.

During her hospitalization the patient was treated with cytoxan and vincristine. Subsequently, leukopenia and thrombocytopenia occurred followed by gram negative sepsis and death.

Post-Mortem Examination: Post-mortem examination disclosed neuroblastoma in the posterior mediastinum with extensive invasion of the right lung, superior mediastinum, the posterior aspect of the pericardium and metastases to mediastinal and cervical lymph nodes and bone marrow. The adrenal glands were normal.

Examination of intracranial contents revealed patent venous sinuses. However, tissue around the torcula was thickened, firm, and hyperemic. Histologic sections of the sagittal sinus near the torcula showed infiltration of the wall by a malignant small cell tumor. No other involvement of the nervous system was seen.

Comment: This case demonstrates that metastases to the venous sinuses can manifest themselves with papilledema as the only neurologic sign. This syndrome has been previously reported (15).

In addition, there was clinical evidence of invasion of the lumbosacral plexus.

Case 2. An 11-month-old boy was admitted with a diagnosis of neuroblastoma. Six weeks prior to admission, proptosis and ecchymoses of the right eye developed and a lump formed on the scalp in the right frontal region. Biopsy of the mass revealed neuroblastoma.

Physical examination on admission revealed proptosis of the right eye, a mass in the right frontal area, edema of both lids, and cervical adenopathy. Neurologic examination disclosed pallor of the right optic disc, an unreactive right pupil to light, and a right sixth nerve paresis. The patient was treated with vincristine and radiotherapy to the entire skull. He was discharged improved after two weeks.

Second Admission: The patient was readmitted one month later because of progressive deterioration. Physical examination showed massive adenopathy, right proptosis, splenomegaly, and a mass in the rectal area. X-rays showed a density in the hilar region, and an osteolytic area in the pelvis.

Neurologic examination disclosed bilateral exophthalmos, right more than left, atrophy of the right optic disc, fixation to light of the right pupil, and sixth and seventh nerve pareses on the right side. Cerebrospinal fluid studies revealed one polymorphonuclear leukocyte, protein of 15 mg%, sugar of 72 mg%, and a negative culture. The electroencephalogram was normal. A right carotid angiogram disclosed a right frontal mass with displacement of the anterior part of the sagittal sinus away from the inner table by one centimeter. The patient was treated with cytosine arabinoside, cytoxan, and vincristine but died from gram negative bacterial sepsis after one month in the hospital.

Post-Mortem Examination: Post-mortem examination disclosed the origin of the neuroblastoma to be in the right adrenal gland. There were metastases to the left adrenal gland, liver, pleura, right humerus, left femur and periaortic, peritracheal, supraclavicular, axillary, cervical, peripancreatic, and pelvic lymph nodes.

Examination of the cranial cavity revealed a reddish-black tumor extending up from the base of the skull and involving all the cranial fossae bulging into the brain substance and extending into both orbital cavities.

Comment: This case illustrates the typical presenting findings of metastatic infiltration of the meninges by neuroblastoma. These findings were proptosis with ecchymoses, and cranial nerve palsies including the second, third, sixth, and seventh cranial nerves.

Case 3. A 19-year-old boy complained of a sudden onset of severe low back pain radiating down both legs, followed by anorexia, insomnia, and a 30-pound weight loss in October, 1965. A month later he was admitted to an Army hospital where the following physical findings were noted: temperature of 101°F, bilateral proptosis and axillary adenopathy. Laboratory findings including chest film, bone survey, intravenous pyelogram, gastrointestinal series, liver function tests, sedimentation rate, lumbar puncture, thyroid function tests, and blood cultures were unrevealing. The only finding was a white blood count of 27,000 with 70% neutrophils. The patient continued to be febrile with persistence of anorexia and progressive weight loss. Subsequently, a node biopsy was performed and sent to the Armed Forces Institute of Pathology where a diagnosis of neuroblastoma was made. Nitrogen mustard therapy was given but the symptoms persisted. He was transferred to another military hospital where on examination adenopathy and hepatosplenomegaly were noted. Chest film showed a widened mediastinum. The hematocrit was 19 and the patient received a transfusion.

He was transferred to James Ewing Hospital in December, 1965. At this time he complained primarily of low back pain and weakness of all extremities, especially the legs.

Physical examination revealed bilateral proptosis, axillary adenopathy, hepatosplenomegaly, and weakness of the legs. Neurologic evaluation showed weakness of all extremities, proximal greater than distal, and absent reflexes in the lower extremities. An electromyogram was performed and interpreted as showing evidence of neurogenic disease of the legs and arms. Myelography performed on January 7, 1966 disclosed extradural defects at L₂, L₄, and L₅-S₁. Radiotherapy was given to this region followed by a slow return of motor function. Wasting of the lower extremities with prominent weakness of the right one was noted. A repeat myelogram was performed on February 23, 1966 showing clearing of the previously noted abnormalities.

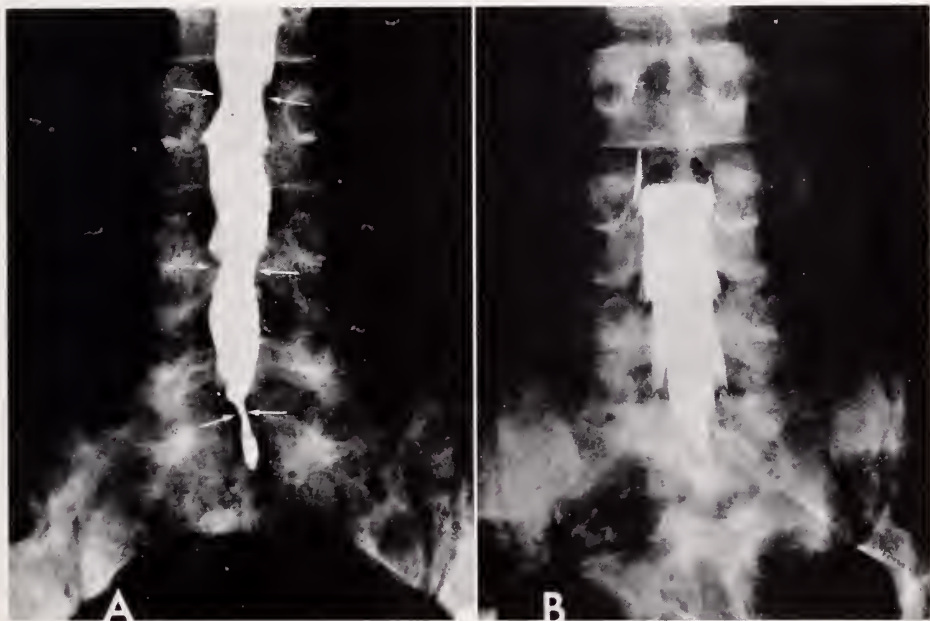


Fig. 1. (Case 3). Myelograms, erect position, anterior-posterior view. A) Before radiotherapy (January 7, 1966). This film demonstrates many extradural neuroblastoma metastases as indicated by arrows. B) After radiotherapy (February 22, 1966). No extradural defects are seen from L₃ to S₁.

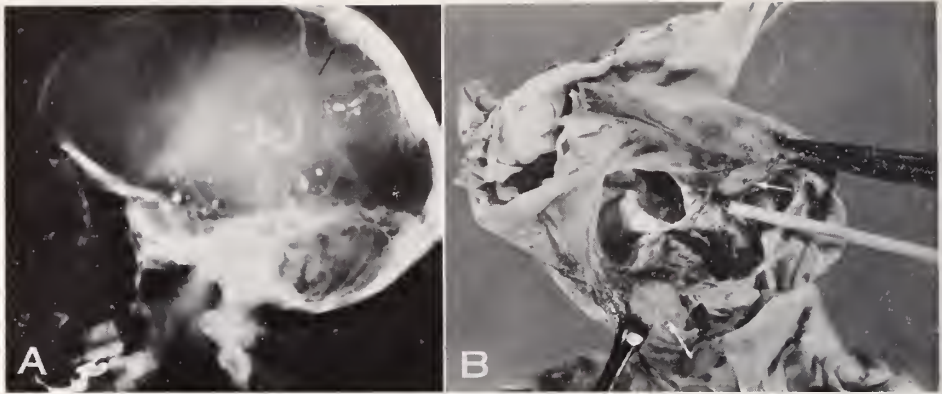


FIG. 2. (Case 3). A) Right brachial angiogram. Late venous phase. Lateral projection. Neuroblastoma metastasis appears as a stain (arrow) adjacent to the superior sagittal sinus. B) Autopsy specimen of meninges: Neuroblastoma metastasis is indicated by the arrows. The superior sagittal sinus is shown by the white pointer.

On May 18, 1966 a neurologic consultation was obtained because of complaints of headaches and double vision. Examination disclosed bilateral papilledema, definite bilateral proptosis, and paresis of adduction and abduction of the right eye. Lumbar puncture revealed an opening pressure of 600 mm of water, clear and colorless fluid, one mononuclear cell, negative cytology for tumor cells, protein of 67 mg%, sugar of 58 mg% and negative serology. Electroencephalogram showed bilateral cerebral dysfunction. Brain scan was normal. Treatment with prednisone 60 mg/day was begun. Examination several days later disclosed only bilateral papilledema. A right brachial angiogram was performed demonstrating a collection of contrast material 1.8 cm to the left of the superior sagittal sinus. Radiotherapy to the brain was begun on May 24, 1966.

On June 6, 1966 neurologic evaluation showed persistence of bilateral papilledema, a left Horner's syndrome, paraparesis right greater than left, moderate weakness in all muscle groups of the upper extremities, and absent reflexes throughout. The patient continued to complain of back pain as well as progressive weakness of the left arm and pain in the left shoulder. Radiation therapy was given to the lumbosacral plexus and cervical spine C₃-C₇.

On July 19, 1966 urinary retention developed along with progressive paraparesis. Examination disclosed a normal mental status and cranial nerves. There was weakness and atrophy of all extremities. In addition, flexion of the hip and all movements of the thigh and knee on the right side were absent. Reflexes were absent in both legs. There was anesthesia to pin and touch in the sacral area on the left side. Several days later there was paraplegia, bilateral Babinski signs, absent position sense to the knees, and a T₁₀ sensory level to pin. Myelogram performed on July 23, 1966 demonstrated a T₇ extradural defect. Radiotherapy was given again but no change in the neurologic status occurred. One month later the patient died with staphylococcal pneumonia.

Post-Mortem Examination: Post-mortem examination disclosed the origin of the neuroblastoma in the right lumbar para-aortic sympathetic chain. Metastases involved the vertebrae, lungs, pleura, celiac, and supraclavicular lymph nodes and right adrenal gland.

Examination of the spinal cord revealed a firm, tan epidural tumor completely encircling the cord at a level of C₅ to T₁.

Examination of the intracranial contents revealed a firm, gray oval mass measuring 2.5 x 2 x 0.7 cm located posteriorly at the junction of the falx cerebri and tentorium cerebelli. The venous sinuses were patent.

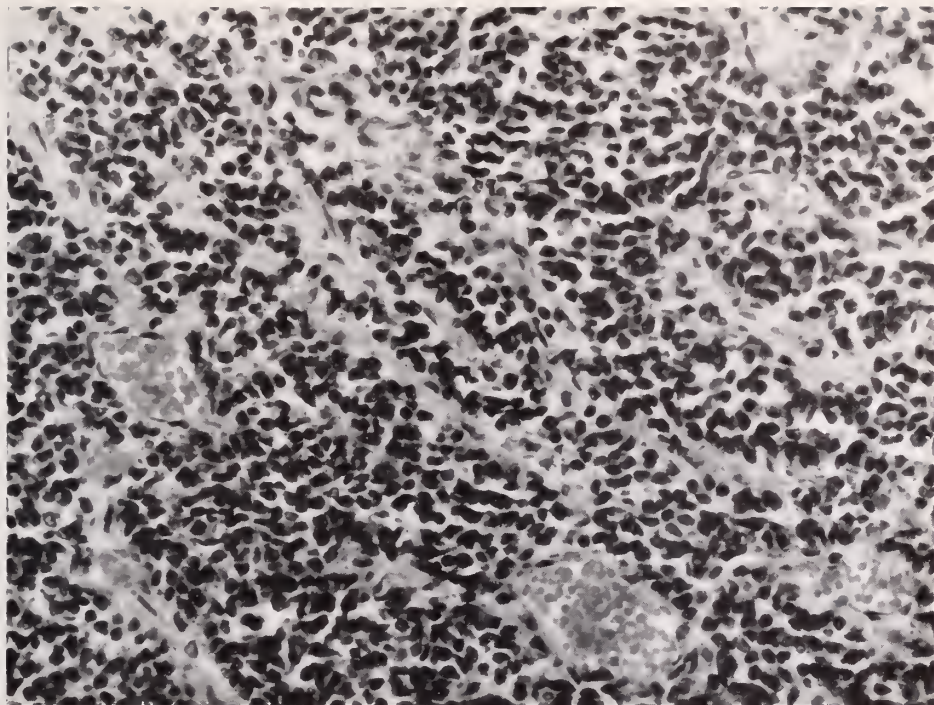


FIG. 3. (Case 3). Microscopic appearance of tumor which originated from the sympathetic ganglia. The tumor is composed of small, rounded cells with little cytoplasm. Section was taken from spinal cord metastasis. (Enlarged from $\times 250$.)

Comment: This patient had evidence of spinal cord and cauda equina disease, as well as involvement of the venous sinus region. Of note was the excellent response of the tumor to radiotherapy with complete disappearance of the lumbosacral extradural defects.

Case 4. A 3½-year-old boy was first admitted with a two-month history of lower abdominal pain. An abdominal mass was palpated and at surgery an inoperable neuroblastoma was biopsied.

Second Admission: Six months later the patient was admitted because of a one-week history of headache.

Neurologic findings included bilateral papilledema, left homonymous hemianopia, left abducens palsy, left facial paresis, left hemiparesis, and a bruit over the right side of the head. Skull films showed separation of the sutures. Lumbar puncture revealed an opening pressure of 600 mm of water, protein of 130 mg%, sugar of 80 mg% and one mononuclear cell.

Several days later the patient became unresponsive to commands and bilateral facial paresis was noted as well as flaccidity of all limbs, and bilateral Babinski signs. A generalized seizure occurred. A right carotid angiogram revealed a deep fronto-temporal stain, a midparietal stain on the right side and a marked shift of the anterior cerebral artery from right to left. Electroencephalogram demonstrated right-sided slowing. Therapy with intravenous urea, dilantin, phenobarbital, chlorambucil, and actinomycin-D was given but the coma progressed and the patient expired.

Post-Mortem Examination: Post-mortem examination disclosed neuroblastoma aris-

ing from retroperitoneal tissue. There were metastases to bone, periadrenal fat, and mediastinal lymph nodes.

Examination of the brain revealed metastatic infiltration of the meninges and parenchymal metastases in frontal and parietal regions on the right side.

Comment: This case demonstrates both meningeal tumor infiltration and intra-axial metastases.

Case 5. A 7-year-old boy was admitted on October 14, 1960 with chest pain and fever which did not respond to antibiotics. One month prior to admission a thoracotomy was performed following discovery of a mass in the left side of the chest. Biopsy disclosed neuroblastoma.

Physical examination on admission revealed a temperature of 102°F, cervical adenopathy, and ronchi over the left side of the chest. Neurologic examination was normal and the patient was treated with penicillin and radiotherapy to the chest.

Second Admission: The patient was admitted because of back pain on March 5, 1961.

Physical examination was negative aside from cervical adenopathy. On neurologic examination, a left homonymous hemianopia, a left hemiparesis, left hyperreflexia, left Babinski sign and tenderness from C₆-T₁₀ were discovered. Lumbar puncture revealed a clear fluid with an opening pressure of 120 mm, normal manometries, and a protein of 23 mg%. Spine films were normal. Electroencephalogram revealed bilateral cerebral dysfunction, right greater than left.

One month later the homonymous hemianopia disappeared but urinary incontinence developed with severe mid-dorsal tenderness. Spine films were again normal. Nevertheless, radiotherapy was given to the spine. Subsequently, all neurologic signs cleared completely. However, the electroencephalogram remained abnormal.

For the next year and a half, the patient was admitted five times with evidence of metastatic disease, particularly to the lungs, and treated with chemotherapeutic agents, viz. cytoxan, actinomycin D, and methotrexate.

Eighth Admission: On December 22, 1962 the patient was admitted with a history of nausea, vomiting, and double vision. Neurologic examination elicited only a left homonymous hemianopia. Lumbar puncture revealed protein of 54 mg%, negative cytology, and five mononuclear cells. Electroencephalogram showed right posterior cerebral dysfunction and a pneumoencephalogram disclosed a shift of the ventricular system from right to left. Radiotherapy to the brain was given. The nausea, vomiting, and diplopia disappeared.

Between January and April, 1963 the patient was admitted on two occasions with abdominal and neck pain. No progression of his illness was noted on either occasion.

In July, 1963 the patient was admitted with a two-day history of headache, nausea, vomiting, and pain in the left side of the neck. Neurologic examination disclosed a left homonymous hemianopia to red color, a left hyperreflexia, left Babinski sign, and tenderness over the lower cervical vertebrae. Spine films showed a lytic lesion at C-3. Lumbar puncture disclosed six mononuclear cells, one polymorphonuclear leukocyte, negative cytology, and protein of 54 mg%. An electroencephalogram showed right posterior cerebral dysfunction. A right brachial angiogram revealed a parietal lesion with a shift of the anterior cerebral artery and internal cerebral vein from right to left.

Follow-up evaluations showed fluctuations of the following neurologic signs: left homonymous hemianopia, upward nystagmus, a left hemiparesis, and a left Babinski sign. The patient was treated with prednisone and further radiotherapy to the brain, but he died after a convulsion.

Post-Mortem Examination: Post-mortem examination disclosed neuroblastoma originating from the posterior mediastinum. Multiple tumor nodules, which were necrotic and contained focal calcification, were found in the left lower lobe of the lung. Metastases also involved the pleura. The adrenal glands were entirely normal.

Examination of the cranial cavity revealed normal meninges. There was a massive metastatic tumor focus with hematoma formation in the right posterior cerebral hemisphere. Tentorial grooving of the hippocampus on the right side and slight grooving on the left side was present.

Comment: This is an example of an intraparenchymal cerebral metastasis. Of note was an eight-month remission of neurologic symptoms in response to radiotherapy.

Discussion

Neurologic manifestations of neuroblastoma are almost exclusively the result of metastatic or invasive disease. However, in the literature there are several case reports of primary neuroblastoma of the central nervous system. A case with detailed pathologic study was described by Miller and Ramsden (5). A 3-month-old baby boy presented with seizures, weakness of the left arm, and swelling in the right parietal area. Surgery revealed cystic cavities within a tumor mass extending to the lateral ventricles and basal ganglia. Histologic sections of the tumor revealed neuroblastoma and 31 months post-surgery there were no neurologic defects or evidence of systemic disease. In 1960, Liss (4) reported a case of a 31-year-old man with neuroblastoma who presented with a one-year history of progressive left hemiparesis. This was followed by left sensory Jacksonian attacks, papilledema, left hemiplegia, and left hemisensory loss. Angiography revealed a right parietal lobe mass. Surgery was performed and followed by radiotherapy. The patient had a 12-year remission before recurrence of symptoms and he died following repeated surgery. At no time was there evidence of metastatic disease elsewhere. Other cases of primary intracranial disease have been reported by Bailey and Cushing (2) and Gyepes and D'Angio (3). Nevertheless, these reports are exceedingly rare. No cases of primary neuroblastoma of the central nervous system were encountered by us.

In clinical reviews of neuroblastoma (1, 6-10) individual incidents of involvement of the central nervous system and frequency of metastatic disease to the brain or spinal cord, have been described. As noted above, there have been no systematic reports of the types of neurologic manifestations. In a review of 205 cases from Memorial Hospital, Dargeon (7) noted that cranial nerve palsies, increased intracranial pressure, proptosis, and cord compression can occur from metastatic disease. Nevertheless, no cases were described and of the 33 reports of metastases to the head and neck the number actually involving the brain or surrounding tissues was not noted. In a review from the Armed Forces Institute of Pathology, 23% incidence of metastases to the skull was reported but involvement of brain or spinal cord was not mentioned (6).

There have been many reports of spinal cord dysfunction manifested generally as cord compression secondary to extradural tumor. Spinal cord involvement may occur by invasion of the spinal canal through the intervertebral foramina or by metastases. Gross, et al (8) report that in 30 cases of cord neoplasm in children six were extradural neuroblastoma. Grant and Austin (13) note that of 30 cord tumors, one was an extradural and one an extra-

medullary intradural neuroblastoma. This is the only report of intradural extramedullary metastasis encountered. In other similar series reported by Hamby (14), Ingraham and Matson (9), Grant (13), and Anderson (11) comprising a total of 326 cases, 16 were neuroblastoma. The cases described are all in children and there are reports of intraspinal extradural neuroblastoma occurring in the neonatal period (10, 12).

Involvement of the brain has been reported less frequently. In a review of 217 cases at Children's Hospital in Boston, Gross et al (8) report metastatic disease to skull and brain in 25% of the cases and to the pituitary gland in 2%. No further statement as to the number actually involving the brain was made. In the neonatal period the reported incidence of intracranial metastases among patients with neuroblastoma is 6.5% (10). Ingraham and Matson (9), in a series of 313 consecutive intracranial lesions, noted four neuroblastomas.

The 36 cases of neuroblastoma with neurologic manifestations seen by the authors are the largest series of its kind. Of these cases 24 are in males and 12 in females. The ages range from 8 months to 21 years. Twenty-two of the cases have pathologic confirmation of the clinical impression of the site of involvement by either post-mortem examination or surgery. In three cases neuroradiologic data without pathologic confirmation indicated the site of the metastatic lesion. In the remaining 11 cases clinical examination and plain x-rays were relied upon to determine the anatomic locus of the lesion. Proved localization was divided into the following gross areas: cerebral meninges and venous sinuses (14 cases); spinal cord (13); roots (7); which includes cauda equina (5); cerebrum (6); plexus (3). Many of these patients had multiple areas of involvement, thus bringing the total to a figure greater than 36. Eight patients were excluded from the above anatomic summary because of lack of sufficient data to place them definitely in one of the above locations. However, all these patients had evidence of intracranial disease.

Neuroblastoma has a definite predilection for infiltration of the meninges and venous sinuses. The meningeal infiltration often results in proptosis and periorbital ecchymoses, and cranial nerve disease. An example is given in Case 2. Spinal fluid examination revealed elevated protein, rarely an increased cell count, negative cytology for tumor cells and no cases of meningeal sarcomatosis. Occasionally the dural tumor enlarged to act as a space-occupying cerebral lesion by compression, or extended through the dura to invade the cerebrum. There were four cases of tumor involving the intracranial venous sinuses which were confirmed by post-mortem examination, and one suspected case. This has been described before by one of us (15) in a series of six patients, two with neuroblastoma, three with Ewing's sarcoma, and one with carcinoma of the cervix. The clinical syndrome includes papilledema, frequently with marked venous engorgement, occasionally dilated scalp veins, and a normal ventricular system.

Intraparenchymal cerebral metastases are not common in neuroblastoma and were seen only in six cases. Their clinical presentation did not differ from other types of metastatic disease.

Spinal cord metastases (13 cases) are common and occurred as extradural deposits which occasionally were associated with bony disease. In this series, two cases showed bony abnormalities related to the locus of neurologic disease.

Spinal root disease (seven cases) occurred by invasion or metastases and most frequently affected the cauda equina region.

Involvement of brachial or lumbosacral plexus is rare, occurring usually by direct extension. Only three cases were seen.

TABLE I
Areas Involved by Neuroblastoma

Case No.	Cerebrum	Cerebral meninges	Venous sinuses	Posterior fossa	Spinal cord	Roots	Plexus
1		+	+				+
2	+	+					
3		+	+		+	+	
4	+	+					
5	+						
6	Intracranial undetermined site						
7		+				+	
8		+	+				
9						+	
10					+		
11		+			+		
12					+		
13		+					
14						+	+
15	Intracranial undetermined site				+		
16	Intracranial undetermined site				+		
17		+	?				
18		+	+				
19	Intracranial undetermined site						
20	Intracranial undetermined site						
21	Intracranial undetermined site				+		
22					+		
23		+					
24						+	
25	Intracranial undetermined site						
26		+			+		
27							+
28					+		
29	+						
30					+		
31					+		
32						+	
33	+	+			+		
34		+					
35	Intracranial undetermined site						
36	+					+	

TABLE II

Anatomic localization	Number of cases
Meninges and venous sinuses	14
Spinal cord	13
Roots	7
Cerebrum	6
Plexus	3
Posterior fossa	0
Intracranial, site undetermined	8
Patients with multiple areas involved	11

Treatment is a complex subject and is difficult to deal with in this report. Most of these cases had a combination of systemic chemotherapy and radiotherapy to focal areas of tumor growth. Our data would definitely support the notion that these tumors are radiosensitive and that excellent temporary remission of symptoms resulting from central nervous system disease is possible. Examples are shown in Case 3, with disappearance of a myelographic defect, and Case 5, where at least an eight-month remission was obtained in the presence of a cerebral metastasis. Generally, patients with neuroblastoma succumbed to metastases in the liver and lungs and not to the central nervous system disease.

Summary

Neurologic manifestations of neuroblastoma in 36 patients are presented. Five representative patients are discussed in detail.

Fourteen patients had infiltration of the cerebral meninges and/or venous sinuses. The clinical signs of meningeal infiltration were commonly proptosis, periorbital ecchymoses, and cranial nerve signs and symptoms. Clinical signs of invasion of the venous sinuses were papilledema, often with marked venous engorgement, and occasionally dilated scalp veins.

Thirteen patients had extradural metastases to the spinal cord, seven had spinal root involvement from invasion or metastases, six had parenchymal cerebral metastases, and three had involvement of the lumbar or brachial plexus. The clinical symptoms and signs of these patients were similar to those caused by other malignant tumors involving the same anatomic loci.

The central nervous system metastases responded well to radiotherapy in several cases and most patients succumbed to metastatic disease involving other systems.

References

1. Bill, A. H., et al: Common Malignant Tumors of Infancy and Childhood, *Pediat Clin N Amer* 6:1197, 1956.
2. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group, Lippincott Co., 1926, 43, 91, 93.

3. Gyepes, M. T., and D'Angio, G. J.: Extracranial Metastases from Central Nervous System Tumors in Children and Adolescents, *Radiology* 87:55, 1966.
4. Liss, L.: Neuroblastoma (Malignant Gangliocytoma) of the Parietal Lobe, *J Neurosurg* 17:520, 1960.
5. Miller, A. A., and Ramsden, F.: A Cerebral Neuroblastoma with Unusual Fibrous Tissue Reaction, *J Neuropath Exp Neurol* 25:328, 1966.
6. Stowens, D., (MC) U.S. Army: Neuroblastoma and Related Tumors, *AMA Arch Path* 63:451, 1957.
7. Dargeon, H. W.: Neuroblastoma, *J Pediat* 61:456, 1962.
8. Gross, R. E., Farber, S. and Martin, L. W.: Proceedings—Neuroblastoma Sympatheticum. A Study and Report of 217 Cases, *Pediatrics* 23:1179, 1959.
9. Ingraham, F. D., and Matson, D. D.: *Neurosurgery of Infancy and Childhood*, Springfield, Ill.: C. C Thomas, 1954, pp. 345-369.
10. Schneider, K. M., Becker, J. M., and Krasna, I. H.: Neonatal Neuroblastoma, *Pediatrics* 36:359, 1965.
11. Anderson, F. M., and Carson, M. J.: Spinal Cord Tumors in Children, *J Pediat* 3:190, 1953.
12. Elefant, E., Vojta, V., and Benes, V.: Intraspinal Neuroblastoma in a Newborn Baby, *Arch Dis Childhood* 33:212, 1958.
13. Grant, F. C., and Austin, G. M.: The Diagnosis, Treatment and Prognosis of Tumors Affecting the Spinal Cord in Children, *J Neurosurg* 13:535, 1956.
14. Hamby, W. B.: Tumors in the Spinal Canal in Childhood, *J Neuropath Exp Neurol* 3:397, 1944.
15. Mones, R. J.: Increased Intracranial Pressure due to Metastatic Disease of Venous Sinuses, *Neurology* 15:1000, 1965.

Received for publication August 8, 1968

Multiple Myeloma Involving the Extrahepatic Biliary System

ARTHUR B. ABT, M.D., AND LUDWIG M. DEPPISCH, M.D.

Introduction

Multiple myeloma is a neoplastic disease characterized by production of abnormal immunoproteins and a diffuse or tumorous proliferation of plasma cells. The plasma cell tumors of this disease occur according to classical descriptions in one or multiple sites within the skeletal system. However, in multiple myeloma, involvement of extraosseous organs is not rare (1-6). Indeed, extramedullary lesions can represent, clinically or at autopsy, the first or the predominant feature of this disease (7, 8).

The following report presents necropsy findings of a patient with multiple myeloma and extensive extramedullary localization.

Case Report

C.C., a 53-year-old single white female school teacher was admitted to the surgical service of The Mount Sinai Hospital in June, 1966, for an elective cholecystectomy. Roentgenologic examination of the gallbladder in April, 1966, detected many small stones. On admission, the hemoglobin was 8.7 gm per 100 ml. Urinalysis revealed 4+ proteinuria. Surgery was cancelled to evaluate the anemia and proteinuria. Bone marrow aspiration revealed a cellular marrow with normal megakaryocytes and marked infiltration with plasma cells (38%), and plasmablasts, consistent with multiple myeloma. X-ray study of the skeletal system showed diffuse osteoporosis without lytic lesions. Bence-Jones protein was present in the urine to the extent of 8 gm per liter. Total serum protein was 5.8 gm, albumin 3.11 gm, α_1 globulins 0.28 gm, α_2 globulins 0.64 gm, beta globulins 0.92 gm, and gamma globulin 0.85 gm per 100 ml. The blood urea nitrogen was 13 mg per 100 ml. Treatment was started with melphalan and testosterone. The patient was discharged on June 27, 1966.

During the following six months she did well except for bone pain. A persistently low hemoglobin necessitated frequent transfusions. She was readmitted in January, 1967, for symptoms of pneumonia, and was successfully treated with antibiotics.

In April, 1967, the patient had increased pain in her right hip, left knee, and lower back. She was readmitted to the hospital with symptoms of pneumonia. The liver was palpable 3 cm below the right costal margin. X-ray examination showed bilateral pleural effusions, segmental atelectasis, lytic lesions of many ribs and the left humerus, and wedging of several dorsal and lumbar

From the Department of Pathology, Mount Sinai School of Medicine, New York, New York 10029.

This investigation was supported by Grant No. 2 TI GM 115-07 from the National Institutes of Health, U. S. Public Health Service.

vertebrae. Four plus proteinuria was present. Total protein was 4.3 gm, albumin 2.4 gm, α_1 globulin 0.22 gm, α_2 globulin 0.54 gm, beta globulin 0.85 gm, and gamma globulin 0.27 gm per 100 ml. Platelet count was 66,000. The pleural effusions contained lymphocytes and many plasma cells. Cultures for bacteria, fungi, and acid fast organisms were negative. Bone marrow aspirates contained 61 per cent plasma cells; many were immature and many were multinucleated with great morphologic variation. Cyclophosphamide was substituted for melphalan. She received transfusions, became afebrile, and was discharged on May 20, 1967.

The final admission occurred on June 27, 1967, because of back pain and shortness of breath. Bilateral pleural effusions contained many plasma cells. Laboratory findings at this time included hemoglobin 7.9 gm per 100 ml, white cell count 6,500 with neutrophils 31 per cent, bands 14 per cent, lymphocytes 40 per cent, monocytes 13 per cent, platelets 174,000, urea nitrogen 42 mg, total bilirubin 7.6 mg, uric acid 14.1 mg, creatinine 2.7 mg per 100 ml, alkaline phosphatase 55 King-Armstrong units, and SGOT 50 units. Repeated thoracenteses were necessary for recurrent pleural effusions. One week after admission congestive heart failure developed, and a week later she became semicomatose and hypotensive. A serum specimen obtained one day prior to her death on July 15, 1967, showed, for the first time, a monoclonal spike in the beta globulin range (2.93 gm) on serum protein electrophoresis.

Autopsy Findings

Necropsy examination was performed 12 hours after death. There was conspicuous scleral icterus but no palpable adenopathy. Each pleural cavity contained approximately 700 cc of serosanguineous fluid. Several firm white nodules, measuring up to one centimeter in diameter, were seen on the parietal pleura bilaterally. The abdomen was flat and no fluid was present.

The heart weighed 220 grams and was grossly unremarkable. The right lung weighed 500 grams and the left 460 grams; they were moderately congested. The liver was enlarged to 2,500 grams, of normal shape, and yellow in color. Bile stasis was not grossly apparent. On cut section, multiple white nodules were seen throughout the parenchyma, the largest measuring 3 mm in diameter. Small areas of hemorrhage were frequent, adjacent to the nodules. The wall of the gallbladder was thickened and its lumen contained multiple black stones measuring up to 4 mm in diameter, and a few cc of bile. Protruding into the lumen of the gallbladder were multiple unencapsulated but well demarcated, firm, white nodules measuring up to one centimeter in diameter. These appeared to be submucosal in location with erosion of the overlying mucosal surface. The common hepatic, right hepatic, and common bile ducts contained similar nodules, the largest of which measured approximately 7 mm in diameter (Fig. 1). The ducts were probe patent, not dilated, and free of stones. The spleen weighed 170 grams and was grossly unremarkable. Many periaortic and retroperitoneal lymph nodes were hemorrhagic, the largest measuring 1.5 cm in diameter. The right kidney weighed 120 grams, and the



FIG. 1. Gross appearance of bile ducts and gallbladder showing tumor nodules ($\times 1$).

left 130 grams. Their parenchyma was pale and petechial hemorrhages were scattered over the external surfaces. In the sternum and vertebral column no gross lytic lesions were identified.

On histologic study the bone marrow was largely replaced by a diffuse pleomorphic infiltrate of immature plasma cells which had deeply stained eosinophilic cytoplasm, and relatively large eccentric nuclei. Many of the nuclei had a "cartwheel" arrangement of chromatin material. A moderate number of these cells were binucleate. The surrounding bone tissue showed evidence of both reabsorption and new bone formation.

The liver parenchyma was infiltrated by tumor nodules of varying size involving portal areas, and in some instances, obliterating the portal bile ducts. These nodules were composed of large numbers of both mature plasma cells and plasma cell precursors. Giant and multinucleate forms were numerous. Small groups and individual tumor cells were also noted within hepatic sinusoids. The

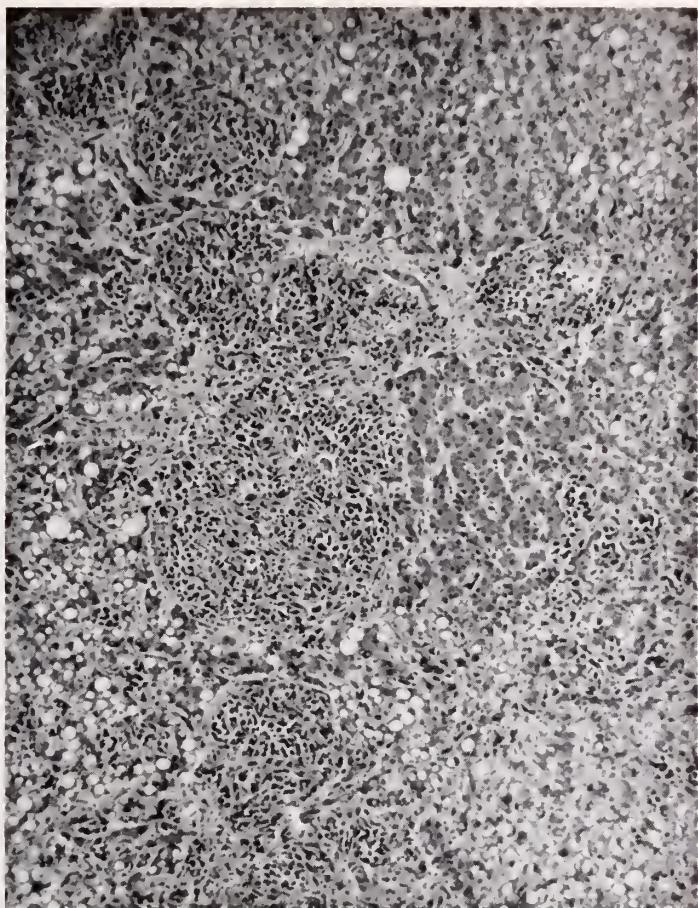


FIG. 2. Liver displaying both nodular and diffuse plasma cell infiltration and moderate steatosis (H & E $\times 40$).

lobular architecture was moderately disorganized. Marked sinusoidal edema was present, and in many areas hepatic cells were arranged in a pseudoacinar pattern. Parenchymal steatosis was diffuse and conspicuous. Intracanalicular cholestasis was extensive, and predominantly centrilobular (Fig. 2).

The gallbladder and extrahepatic bile ducts were infiltrated by nodular masses of similar appearing plasma cells which involved all layers of these structures. Much of the mucosa overlying the tumor nodules was eroded (Figs. 3, 4).

The kidneys contained scattered plasma cell infiltrates. A few dense eosinophilic casts were in the distal tubules, and rare peritubular multinucleated giant cells were seen in association with these casts. Congo red and crystal violet stains for amyloid were negative here and in other organs. In addition to the previously described organs, multiple focal infiltrates of plasma cells



Fig. 3. Cross section of common bile duct showing myelomatous infiltrates (H & E \times 10).

were present in the spleen, lymph nodes, heart, pleura, lungs, periadrenal fat, pancreas, and diaphragm. Larger nodular infiltrates were found in the submucosa of the small bowel.

Discussion

Plasma cell tumorous involvement of the gallbladder in multiple myeloma is extremely rare. Only one previous case of gallbladder involvement was reported in an extensive literature review of extramedullary lesions in multiple myeloma (3). It is uncertain whether the narrowing of the extrahepatic ducts produced by these nodules was of clinical significance. No histologic criteria for extrahepatic biliary obstruction were found; bile lakes and bile duct proliferation were absent. It would seem, therefore, that another cause for the patient's jaundice, other than extrahepatic obstruction, was present. Intrahepatic biliary obstruction on a mechanical basis by a diffuse myeloma cell infiltrate (9), or by a solitary plasmacytoma (10) have been described.

Myeloma cell infiltrates have been identified in many extramedullary locations. By far, the most common sites have been the extraosseous hematopoietic system (spleen, liver, lymph nodes) (1, 3, 5). Other organs have less frequently been affected. A partial list would include kidney, lung, pancreas, pericardium, and adrenal (2). Infrequently, unusual extramedullary involvement is an early clinical sign; testicular swelling (7) and multiple skin nodules (8) have been recorded recently.

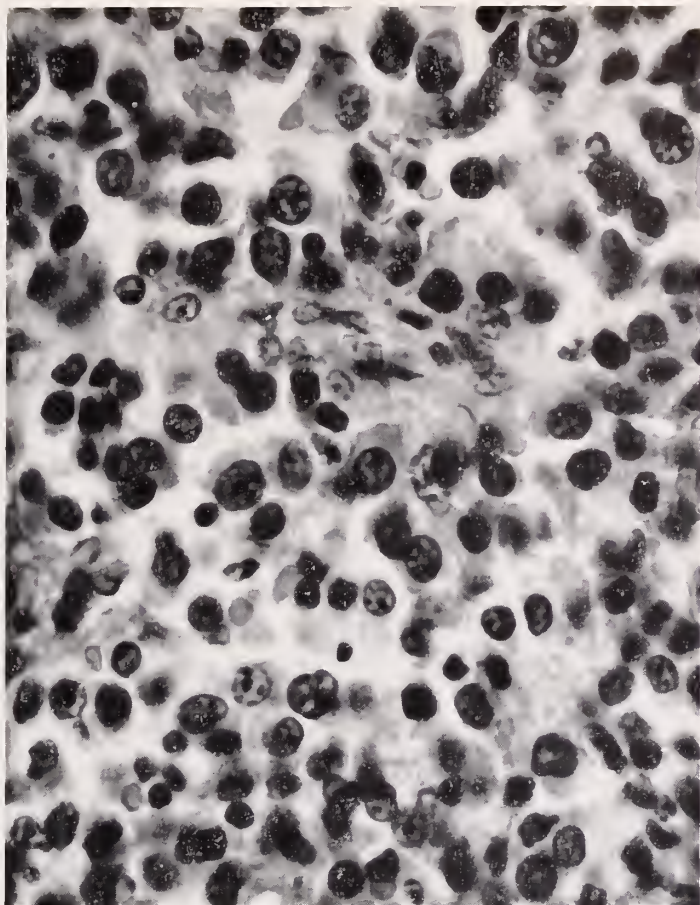


FIG. 4. High power view of gallbladder nodules showing pleomorphic myeloma cells. They display eccentric nuclei, hyperchromatism and enlarged size. Scattered mature plasma cells are seen (H & E $\times 400$).

Several autopsy series of multiple myeloma have been analyzed to determine the exact incidence of extraosseous lesions. Incidents of 50 (4), 58 (2), 70 (5), and 71 (3) per cent have been recorded. Usually, myeloma cell infiltrates have been recognized only microscopically, and have been more diffuse than tumorous (2, 3).

The predominance of extramedullary myeloma lesions in components of the extraosseous hematopoietic system has suggested to some an autochthonous origin as the best explanation (3, 11). However, in this case, the myeloma cell nodules mimicked the metastatic lesions of a highly malignant neoplasm. This gross pathologic picture, the frequent finding of myeloma cells in the peripheral blood (5), and the occasional involvement of tissues normally lacking components of the hematopoietic system (2, 3, 5, 7, 8, 12), have suggested to others

(1) and to ourselves, that these extramedullary lesions probably represent metastases from a primary neoplasm in bone.

Summary

A case of multiple myeloma with extensive extraosseous lesions, including unusual involvement of the gallbladder and hepatobiliary system is briefly recorded. These lesions did not produce significant constriction of the bile duct, or obstructive jaundice. The significance and the incidence of extramedullary involvement in multiple myeloma is reviewed.

Acknowledgment

The authors wish to acknowledge the assistance and encouragement of Dr. Hans Popper in the preparation of this manuscript.

References

1. Geschickter, C., and Copeland, M.: Multiple Myeloma, *Arch Surg* 16:807-863, 1928.
2. Carson, C., Ackerman, L., and Maltby, J.: Plasma Cell Myeloma. A Clinical, Pathologic and Roentgenologic Review of 90 Cases, *Amer J Clin Path* 25:849-888, 1955.
3. Hayes, D., Bennett, E., and Heck, F.: Extramedullary Lesions in Multiple Myeloma, *Arch Path* 53:262-272, 1952.
4. Innes, J., and Newall, J.: Myelomatosis, *Lancet* 1:239-245, 1961.
5. Churg, J., and Gordon, A.: Multiple Myeloma: Lesions of the Extraosseous Hematopoietic System, *Amer J Clin Path* 20:934-945, 1950.
6. Owen, D.: Multiple Myeloma, *Geriatrics* 20:1048-1065, 1965.
7. Osman, R., and Morrow, J.: Myeloma of the Testicle: A Case Report, *J Urol* 96:352-355, 1966.
8. Levin, H., Freeman, R., Smith, F., and Lane, M.: Multiple Extramedullary Plasmacytomas, *Arch Derm* 96:456-461, 1967.
9. Davis, H., Caron, G., and McKinney, B.: Multiple Myeloma Presenting Clinically as Obstructive Jaundice, *Postgrad Med J* 35:668-670, 1959.
10. Bark, C., and Feinberg, S.: Solitary Plasmacytoma with Obstructive Jaundice, *JAMA* 201:491, 1967.
11. Lowenhaupt, E.: Proliferative Lesions in Multiple Myeloma with Special Reference to Those of the Spleen, *Amer J Path* 21:171-177, 1945.
12. Edwards, G., and Zawadzki, Z.: Extraosseous Lesions in Plasma Cell Myeloma, *Amer J Med* 43:194-205, 1967.

Received for publication August 12, 1968

CLINICO-PATHOLOGICAL CONFERENCE

Azotemia, Proteinuria, Peripheral Vascular Disease, and Fibrothorax in a Male with Mild Diabetes Mellitus

Edited by

FRANKLIN M. KLION, M.D.

A 68-year-old white man was admitted to The Mount Sinai Hospital for pain in the left foot.

For one and one half years he noted swelling of both lower extremities and shortness of breath. He was placed on digitalis therapy and following several episodes of acute thrombophlebitis, was maintained on anticoagulants. Mild azotemia was known for approximately one year. Subsequently, progressive intermittent claudication of the lower extremities developed, and five months prior to admission he noted a purplish macular eruption on the legs. Multiple ulcerated lesions developed shortly before entry. A culture of some of the lesions grew gram-negative organisms.

He was treated for pulmonary tuberculosis many years earlier and was known to have diabetes mellitus for approximately 40 years, controlled by diet. He denied chest pain or hypertension.

He was a thin, chronically ill man. His blood pressure was 130/60. The pulses in both lower extremities were markedly decreased and a purplish macular rash was present over the lower extremities as well as a large odoriferous ulcerated lesion on the medial aspect of the left ankle. The ocular fundi showed two small hemorrhages and old exudates. There was mild distention of neck veins at 10°. Breath sounds were absent in the right chest, and the trachea was deviated to the right. The liver was not enlarged. One observer felt the tip of the spleen. No lymph nodes were palpable. An x-ray of the chest showed a right fibrothorax without evidence of active disease and cardiomegaly, and an electrocardiogram revealed a pattern consistent with an old inferior myocardial infarct and left ventricular hypertrophy. The hemoglobin was 8 gm% and the peripheral smear showed moderate hyperchromia. The white blood cell count ranged between 8,000–14,000/mm³, with a slight shift to the left. The erythrocyte sedimentation rate was 139 mm/hr, and the platelet count was 318,000/mm³. The BUN was 85 mg%, creatinine 3.7 mg%, potassium 5.4 mEq/L, sodium 138 mEq/L, chlorides 106 mEq/L, carbon dioxide 24 mEq/L. The serum albumin was 2.2 gm%, globulin 2.8 gm%, cholesterol 248 mg%, calcium 8.5 mg%, bilirubin 0.3 mg%, and fasting blood sugar 95 mg%. A repeat fasting blood sugar was 125 mg%. The serum protein electrophoresis was normal. Immunoelectrophoresis of the serum revealed a decrease of all immunoglobulins. The urine specific gravity was 1.008. There was moderate proteinuria, and the urinary sediment contained 2 to 3 red blood cells per high power field, and white blood cell casts. A 24 hour urine sample contained 3.7 grams of protein per liter. Immunoelectrophoresis of the urine contained the

spectrum of serum proteins without an excess of light chains. A urine culture grew enterococcus and proteus mirabilis. The sternal bone marrow was cellular. The myeloid erythroid ratio was 4:1. Stainable iron within the marrow was considered normal. The serum iron was $21 \mu\text{g}\%$, and total binding capacity was $210 \mu\text{g}\%$. Sputum, bone marrow, and urine cultures for acid fast organisms were negative.

Despite bed rest, his dyspnea increased and the sputum became purulent. A low grade fever present since admission persisted. He was treated with broad spectrum antibiotics, isonicotinic acid hydrazid and paraamino salicylic acid without significant improvement. He became progressively obtunded and died on the 23rd hospital day.

*Dr. Richard P. Wedeen**: This man was admitted to The Mount Sinai Hospital because of pain in his left foot. The pain apparently arose from a large ulcerated lesion on his left ankle. It is reasonable to assume these lesions were related to stasis dermatitis. In view of this history of recurrent thrombophlebitis and peripheral edema, it is not surprising that such lesions became ulcerated and infected, since the patient was diabetic and had symptoms related to peripheral vascular insufficiency. Recurrent thrombophlebitis always raises the possibility of malignancy, but there is no other evidence to suggest a neoplasm. More pertinent to the patient's diagnosis and clinical course is the evidence of significant pulmonary disease.

We are told that the patient had tuberculosis for which he received drug therapy many years before. Breath sounds were absent over the right chest, and the trachea was deviated to the right. The x-rays showed extensive fibrotic disease of the right chest, and deviation of the thoracic structures to the right. The scalloped appearance of the right lung border also suggests atelectasis. Partial atelectasis of the lung was presumably due to the old endobronchial tuberculosis, although it could be of more recent origin. In any case, it seems quite likely that he had a chronic infectious process in the right lung. However, active tuberculosis is unlikely in view of the negative cultures. The clinical and radiologic features are consistent with bronchiectasis, although some of the pulmonary symptoms could be due to congestive heart failure.

The electrocardiogram showed evidence of an old myocardial infarction and left ventricular hypertrophy, presumptive evidence of arteriosclerotic heart disease. However, the heart was not enlarged and there was only mild distention of neck veins with the patient 10° from the horizontal. The house physicians apparently did not feel he was in congestive failure, since they undertook antibiotic rather than cardiotonic or diuretic therapy. In patients with respiratory and cardiac disease, the diagnosis of mild congestive failure may be difficult. Differentiation is important in interpreting the pulmonary findings, and is of considerable importance in evaluating the renal dysfunction.

Since the patient was not oliguric, the heavy proteinuria suggested a ne-

*Assistant Professor, Department of Medicine, Mount Sinai School of Medicine, New York.

phrotic syndrome. In the presence of congestive heart failure, one might have had difficulty differentiating the azotemia and proteinuria associated with heart failure from intrinsic renal disease. In the absence of congestive heart failure, these renal findings must be explained by glomerular disease. White cell casts and significant colonies of enterococcus and proteus mirabilis cultured from the urine are compatible with pyelonephritis.

While pyelonephritis may well have contributed to the renal insufficiency, it would not be expected to account for the heavy proteinuria. Obstructive uropathy and a secondary urinary tract infection also should be considered. Other diseases associated with severe proteinuria include acute and chronic glomerulonephritis, idiopathic tubular necrosis, allergic and idiosyncratic responses to chemicals, renal vein thrombosis, and vasculitis. In the absence of a characteristic history, hypertension or noncardiac salt and water retention, it is difficult to consider any of these diagnoses. The low grade fever, anemia, splenomegaly, retinal hemorrhages and exudates, septic skin ulcers, and heart disease, raise the possibility of subacute bacterial endocarditis. In the absence of typical skin lesions, a heart murmur, and positive blood cultures, this diagnosis appears unlikely but cannot be excluded.

The history of diabetes mellitus presents an even more perplexing problem. We are told that the diagnosis was established when he was only 28 years of age, but the laboratory data substantiating the diagnosis are not convincing, and azotemic diabetic nephropathy is usually associated with hypertension. Although a normal fasting blood sugar in the presence of mild diabetes is not uncommon, the very modest glucose intolerance could be explained by low carbohydrate intake, azotemia, liver disease, or a nonfasting state. It is well known that the vascular disease in diabetes may not parallel the defect in carbohydrate metabolism. Thus, retinitis, glomerulitis, and generalized arteriosclerosis, may be found in the presence of only minimal glucose intolerance or even in the prediabetic state when no glucose intolerance is found.

The presence of retinitis, glomerulitis, arteriosclerotic heart disease, peripheral arteriosclerosis, atherosclerosis, skin infection, tuberculosis, and pyelonephritis suggests this patient had diabetes, although the typical retinal microaneurysms were not seen. Although the patient may have diabetes, it is unusual though possible to have severe diabetic nephropathy with very mild disease.

Amyloidosis also may cause renal failure and severe proteinuria. There is no suggestion of primary amyloidosis; that is amyloidosis unassociated with another disease. Similarly, the diagnosis of the tumorous and familial form cannot be made. Multiple myeloma is associated with amyloidosis in about 15 per cent of the cases, but the absence of plasmocytosis, a globulin spike on serum electrophoresis, light chains or Bence-Jones' proteinuria, or hypercalcemia, exclude this diagnosis. Although the term "secondary amyloidosis" has been widely criticized because of the erroneous connotation of organ specificity, it is a useful term to denote a variable syndrome associated with chronic and inflammatory diseases and certain tumors. There is no suggestion of Hodg-

kin's disease or hypernephroma, the tumors most frequently associated with amyloidosis. On the other hand, tuberculosis, diabetes mellitus, chronic skin ulcers and bronchiectasis, are frequently associated with amyloidosis. The absence of hypertension supports the diagnosis of amyloidosis primarily by making other causes of renal failure less likely. The elevated sedimentation rate is consistent with chronic infection, and hypergammaglobulinemia which was absent in this patient, is not essential for the diagnosis of amyloidosis.

The lowering of serum globulins probably resulted from a glomerular leak. The anemia also seems to be best explained on the basis of chronic infection and azotemia. Thus, although the serum iron was low, iron was present in the marrow so that chronic blood loss or hemolysis was unlikely. Thus, amyloidosis is suggested by the presence of azotemia, heavy proteinuria, in the absence of hypertension, and in the presence of chronic pulmonary infection. The diabetes, skin ulcers, splenomegaly, and elevated sedimentation rate support this diagnosis. It is noteworthy that a number of the findings which I have attributed to vascular disease, might also be caused by amyloidosis. These include heart failure with electrocardiographic evidence of myocardial infarction, although the cardiographic pattern in amyloid heart disease is usually that of anterior wall infarction. Purpuric lesions due to vascular amyloid infiltrates are common, and in association with amyloid neuropathy, painful leg ulcers are frequent. Finally, amyloid deposition in the pancreas may produce late onset diabetes. Renal tomograms are helpful since large kidneys are more often found in renal failure due to amyloidosis than from most other causes. Unfortunately, the x-rays of the abdomen did not permit an accurate determination of kidney size.

I should point out that while secondary amyloidosis can explain the renal failure in this patient, it cannot readily account for the funduscopic observations. Amyloid lesions of the cornea and vitreous, and ocular palsies have been described in secondary amyloidosis. Retinal hemorrhage and exudate have been seen only in primary familial amyloidosis. In order to account for the retinal hemorrhage and exudates, I considered subacute bacterial endocarditis, but I think they are most likely due to diabetes mellitus. The renal failure in amyloidosis is slowly progressive and usually is the cause of death. Pulmonary infection, heart failure, sepsis or pulmonary embolization, however, may have been responsible for his demise.

In summary, I propose the following diagnoses: 1) amyloidosis; 2) diabetes mellitus; 3) arteriosclerotic heart disease with an old myocardial infarction; 4) generalized arteriosclerosis; 5) tuberculosis probably inactive; and 6) bronchiectasis and pyelonephritis.

*Dr. Laurence Alpert**: At autopsy there was slight peripheral edema, early gangrenous changes of the toes, and multiple small ulcerated lesions over both malleoli.

His heart was enlarged and showed old fibrosis and an old myocardial

* Assistant in Pathology, Mount Sinai School of Medicine, New York.



FIG. 1. Cross section of lung showing large, thick-walled bronchiectatic cavities, fibrosis and atrophy of residual pulmonary parenchyma.

infarction. He also had severe atherosclerosis of the aorta with marked aortoiliac narrowing. The ulcerations of his legs were probably the result of peripheral arterial insufficiency, and may have been aggravated by recurrent thrombophlebitis.

The right lung had to be stripped from the thorax, and the pleura was thickened and there was some compensatory emphysema of the left lung. No pleural effusions were present. The lungs were mildly congested. Because of the history of tuberculosis, the lungs were perfused with formalin before opening. Sections of the right lung showed marked pleural fibrosis, many large thick-walled cysts, and atrophy of the pulmonary parenchyma with marked thickening of the bronchi (Fig. 1). Sectioning of the thick cystic cavities revealed marked ectasia of the bronchi, and an absence of functional pulmonary parenchymal tissue. We were unable to find any foci of active tuberculosis.

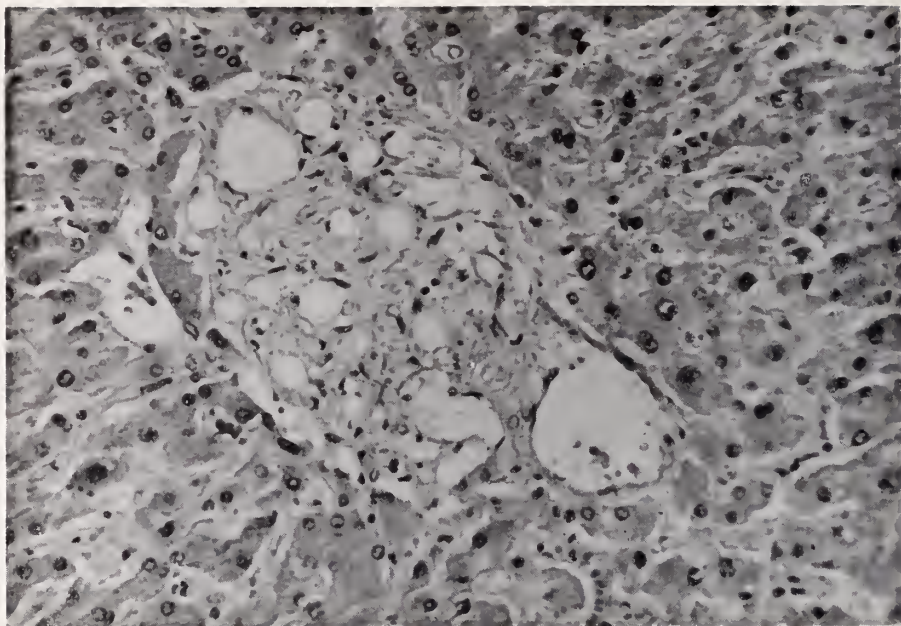


Fig. 2. Paracentral hepatic fat granuloma, representative of multiple ones scattered throughout liver (hematoxylin and eosin, $\times 100$).

The liver was slightly enlarged and weighed approximately 1,900 grams. The architecture was intact. However, grossly, several yellowish flecks were scattered over the surface of the liver. Microscopically, these represented areas of liver cell necrosis. Acute and chronic inflammatory cells replaced the necrotic liver cells, suggestive of sepsis. Stains for fungi and bacteria, however, were negative. In addition, multiple fat granulomas in various stages of organization were found in the portal tracts (Fig. 2). These granulomas consisted of large, swollen fat cells with a mesenchymal reaction. Occasionally, similar granulomas were found in the pericentral areas associated with fibrosis. Fat granulomas are frequently seen in livers of alcoholic and diabetic patients. Perhaps at one time he had a fatty liver. Of more interest were many large, reticuloendothelial cells lying free in the sinusoids containing numerous red cells. The significance of erythrophagocytosis in the patient is unclear. Possibly it is related to chronic infection with secondary hyperplasia of reticuloendothelial system.

The spleen was enlarged and soft. On cross section, there was reticuloendothelial hyperplasia, as well as numerous polymorphonuclear leukocytes in the red pulp, suggesting sepsis.

The pancreatic islets were normal (Fig. 3), showing none of the stigmata of diabetes mellitus.

A caseous lesion was found in the left testis.

A similar caseous lesion was present in the left kidney (Fig. 4). On mi-

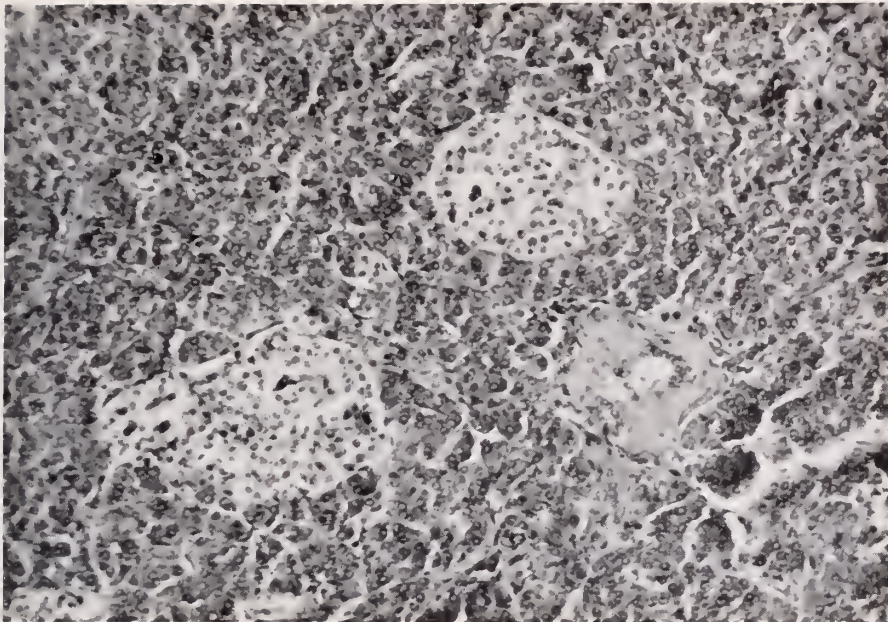


FIG. 3. Section of pancreas showing normal islets of Langerhans (hematoxylin and eosin, $\times 100$).



FIG. 4. Left kidney showing cavitory lesion in lower pole containing caseous material. Remainder of kidney shows marked thinning of cortex with indistinct corticomedullary junction.

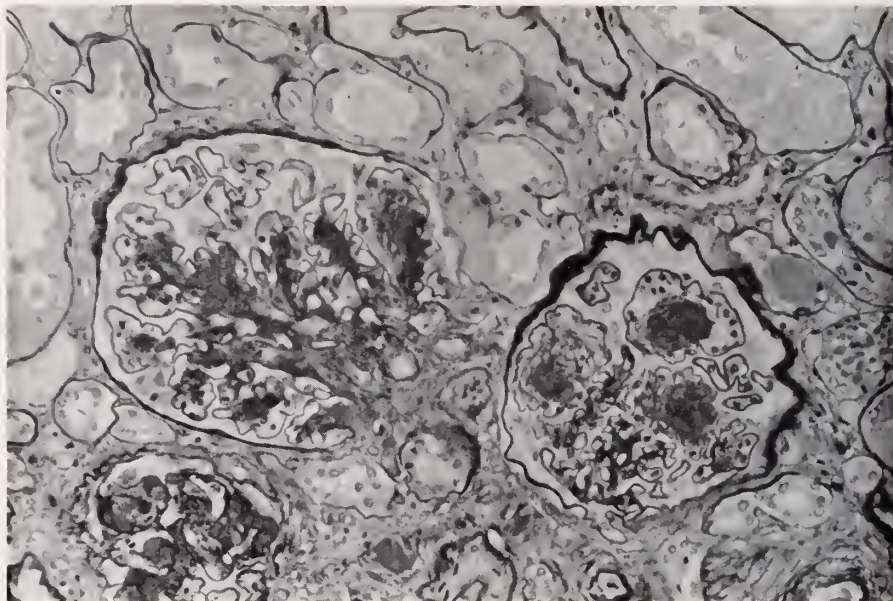


FIG. 5. Section of kidney showing adjacent glomeruli exhibiting the two characteristic patterns of diabetic glomerulosclerosis; thickening of the mesangial matrix in a finger-like distribution (left), and nodular deposits within glomerular capillaries (right) (hematoxylin and eosin, $\times 100$).

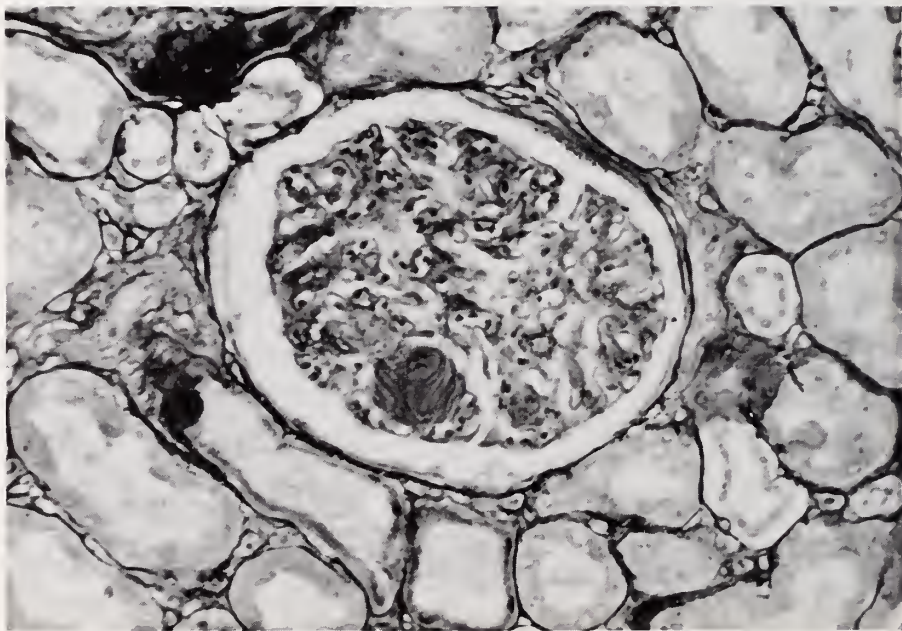


FIG. 6. Acellular nodular deposit revealing laminations (Wilder's stain for reticulum, $\times 400$).

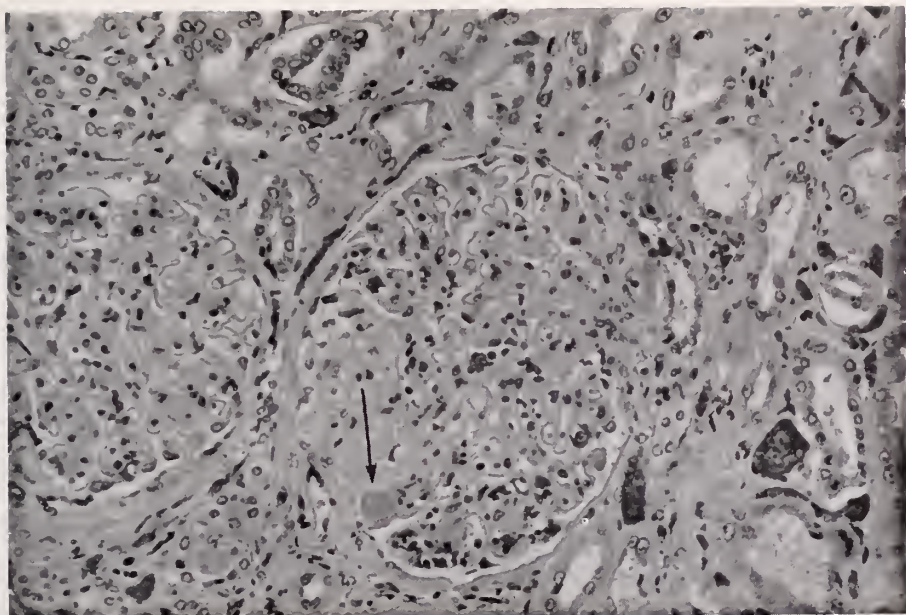


Fig. 7. Exudative nodular lesion (arrow) (hematoxylin and eosin, $\times 100$).

gross examination, there was little or no inflammatory response, and numerous stains for acid fast bacilli were negative. These lesions represent healed tuberculous foci which, for some reason, failed to fibrose though the organisms were no longer present. The kidneys were granular in appearance and the cortical medullary junction was obscured. The right kidney was larger, weighing 200 grams and also had a finely granular consistency. Both kidneys showed evidence of acute pyelonephritis. Numerous polymorphonuclear leukocytes infiltrated the collecting tubules, the interstitium and the glomerular capillaries. However, the most striking finding in the kidneys were lesions characteristic of advanced diabetic glomerular sclerosis or Kimmelstiel-Wilson's disease. There was marked thickening of the mesangial matrix and the capillary walls by a homogenous, acellular, somewhat laminated material (Fig. 5). A silver stain showed the laminated appearance of the typical nodular glomerular lesion (Fig. 6), suggesting the material is formed in layers over a long period of time. In addition to nodular and diffuse lesions, a third lesion typical of diabetic glomerular sclerosis, was also present, namely the exudative nodule (Fig. 7). Ultrastructural studies have clearly shown the thickening of the capillary basement membrane and increase in mesangium in diabetic nephropathy. In the nodular and diffuse lesions, the electron dense material spreads out, pushing the capillaries aside. Large accumulations lead to nodule formation. The exudative lesion, in contrast, consists of electron dense material of different densities which, when deposited, fills and occludes the entire lumen. This material is not specific for diabetes, but rather it is seen wherever there is increased glycoprotein synthesis.

The chief anatomic lesion was diabetic glomerulosclerosis of the nodular, diffuse, and exudative types. It is interesting that such severe diabetic glomerulosclerosis occurred in a man who had extremely mild diabetes with no changes in the pancreatic islets, and who received insulin for only a very short time, suggesting that the lesion is not related to insulin treatment as some have thought in the past. In addition, there was acute pyelonephritis which contributed to his terminal renal failure, and septicemia probably secondary either to the lower extremity ulcers, or to pyelonephritis. He had inactive tuberculosis, with fibrosis of the right lung, kidney, and testes. Finally, there was severe arteriosclerotic cardiovascular disease.

Final Diagnoses: 1. DIABETIC GLOMERULOSCLEROSIS (KIMMELSTIEL-WILSON'S DISEASE). 2. ACUTE PYELONEPHRITIS. 3. HEALED TUBERCULOSIS OF RIGHT LUNG; INACTIVE TUBERCULOUS CAVITARY LESIONS OF TESTES AND RIGHT KIDNEY. 4. SEPTICEMIA, TERMINAL.

Unusual Problems in Surgery

HENOCHE-SCHÖNLEIN PURPURA

Although Henoch-Schönlein purpura is primarily a medical disease of young children, perplexing problems requiring keen surgical judgment may arise in connection with the gastrointestinal manifestations. An illustrative case together with the salient features of this multifaceted disease are presented.

E.H. #433759. A 13-year-old white boy came to the emergency unit at Elmhurst Hospital on January 3, 1968 complaining of epigastric and periumbilical pain for two days. The pain grew progressively worse and was associated with nausea and anorexia but no vomiting or diarrhea. He had imbibed 10 glasses of beer before his symptoms began. There was a history of an upper respiratory infection and sore throat one week prior to his current illness. Abdominal examination revealed moderate periumbilical tenderness without any muscle spasm. Normal bowel sounds were heard. Temperature and pulse were normal. A provisional diagnosis of gastritis was made and the patient was given an antacid with instructions to return if symptoms persisted.

He returned the following day complaining of persistent pain and several episodes of vomiting. He had no bowel movement for two days. The abdomen was soft and exhibited moderate epigastric and periumbilical tenderness. Some deep tenderness and questionable muscle guarding in the right lower quadrant was noted. The bowel sounds

were normal and rectal examination disclosed the presence of soft brown stool. The remainder of the physical examination, past medical history, and family history were not remarkable. The patient was admitted with a diagnosis of gastroenteritis for observation as a possible case of acute appendicitis.

The findings on admission were: temperature, 98.6; pulse, 78; blood pressure, 110/60; urine, negative except for a trace of acetone; hematocrit, 43%; white blood count, 16,400, polys 78, lymphs 18, monos 5; serum sodium 136 mg%, potassium 4.8 mg%, chloride 91 mg%, protein 5.8 gm%, albumin 2.9 gm%, and glucose 140 mg%.

X-ray of the chest was normal. Plain x-rays of the abdomen disclosed two minimally distended small bowel loops in the right midabdomen adjacent to the ascending colon. This was interpreted as a possible response to adjacent inflammation in the right midabdomen or lower abdomen, but no more specific statement could be made.

The day after admission, the signs and symptoms persisted unchanged. The white blood count was 11,000 with a normal differential distribution. The evening temperature rose to 101 degrees and returned to normal the following day. However, because of the persistent symptoms without any improvement, the patient was explored on January 6, 1968. Upon entering the abdomen a small amount of serous fluid was noted and a culture

was performed (no growth). The appendix appeared essentially normal. The terminal 3 centimeters of ileum was thickened, edematous, and inflamed. The remainder of the small intestine appeared normal. The pathology of the ileum was interpreted as an acute terminal ileitis. Appendectomy was performed. Microscopic examination of the appendix revealed mild focal areas of inflammation with an area near the tip exhibiting ulceration of the mucosa and hemorrhage of the submucosa.

Postoperatively the first stools were loose and bloody. The urine contained many red and white blood cells. On the ninth postoperative day a macular purpuric eruption appeared on the upper and lower extremities. On the 11th postoperative day a small bowel contrast roentgenogram showed the distal ileum to be narrowed and thick walled with "cobblestoning" of the mucosa. A more proximal segment of jejunum exhibited mucosal edema and spiculation of its borders. The findings were compatible with a clinical diagnosis of regional enteritis or Schönlein-Henoch purpura (Figs. 1, 2). The patient left the hospital 13 days after operation and was reexamined in the Outpatient Clinic two weeks later. He had no complaints. The abdomen was soft, not tender, and exhibited no organomegaly. Complete blood studies were normal. There was a fading petechial and purpuric eruption of the extremities. Urine examination still revealed albuminuria, numerous red cells, and numerous white cells. The findings of a nonthrombocytopenic purpura, skin eruption, abdominal symptomatology, and hemorrhagic

gastrointestinal and urinary phenomena indicated that the diagnosis was most probably Schönlein-Henoch purpura. Note should be made of the similarity of the small bowel roentgenograms to that which is seen in granulomatous enteritis, amyloidosis, Whipple's disease, and sprue (3).

Etiology

The varied manifestations of Henoch-Schönlein's anaphylactoid purpura have been explained as a result of local or generalized vascular damage. The initiating factor is not definitely known. 90 per cent of patients have evidence of fever or infection prior to or at onset of symptoms, yet no specific organism is involved. Rarely, specific allergens seem to be implicated e.g. insect bites, egg, chocolate, and milk. 75 per cent of cases are under the age of seven, mostly males.

Clinical Considerations

In their series of 131 patients, Allen and associates reported the following signs and symptoms in descending order of occurrence: skin eruption, fever, joint manifestations, preceding infection, abdominal pain, guaiac positive stools, extremity edema, melena, hematuria, scalp edema, and hematemesis (1).

The skin rash is characteristic and essential for diagnosis in almost all cases. It is often urticarial in onset and then replaced by red macular lesions which turn brown. Ecchymoses may appear. The lower extremities and buttocks are most commonly involved. In half of the cases, the rash is the first symptom.

Joint tenderness or swelling is noted



Fig. 1. Contrast roentgenogram shows a grossly distorted small bowel pattern with thickening of the walls as demonstrated by the increased radiolucent space between the loops (lower arrow) and prominent thick folds (upper arrow).

in $\frac{2}{3}$ of the cases, most often in the knees and ankles. The involvement is usually transitory, leaving no residua.

Soft tissue edema, exhibited as lo-

calized swellings of the subcutaneous tissues, occur most often in the hands, feet, scalp, and periorbital region.

Gastrointestinal symptoms and



Fig. 2. Contrast roentgenogram shows a thick-walled narrow segment of terminal ileum with "cobblestoning" of the mucosa.

signs are encountered in more than $\frac{2}{3}$ of the patients (i.e. abdominal colic, vomiting, melena, and hematemesis). They are more frequent and serious in older children, and, together with the renal involvement, they are responsible for most of the morbidity and mortality of this disease. More than

eighty per cent of patients with gastrointestinal involvement have abdominal pain and some evidence of hemorrhage from the gastrointestinal tract. The hemorrhage is rarely massive and usually subsides with conservative management.

Renal damage of varying severity

occurs in 40 per cent of all patients. Albuminuria and microscopic hematuria, usually occurring together, are the most frequent findings. Gross hematuria, hypertension, azotemia, and oliguria, in descending order of frequency, may also occur; azotemia and oliguria are indicative of more serious damage and may portend a permanent renal impairment. Urine abnormalities may persist from months to years even though the patient appears clinically well.

Other less common manifestations include hemorrhagic edema of the testes and voluntary muscles. Intracerebral hemorrhage may cause convulsions, encephalopathy, and sometimes leads to fatality.

The duration of anaphylactoid purpura ranges widely from a few days to two years or more, with an average of four weeks. 40 per cent of the patients who recover and are completely well have recurrences of the skin eruption (most frequent), abdominal pain, and melena. There is a close correlation between severity and the duration and recurrence of the disease. Children under two years of age have a more widely scattered urticarial type of skin rash and exhibit edema of the scalp and feet more often. However, the disease is generally milder in this age group; the duration is shorter, recurrences are fewer, and there are less frequent gastrointestinal and renal manifestations.

There are no specific laboratory determinations which are helpful in making the diagnosis; some tests are useful in following the course of the disease e.g. hemoglobin, hematocrit, stool, and urine examinations. Throat cultures are significantly positive in over 80 per cent; the most frequent

organisms are hemolytic *Staph aureus*, Beta hemolytic streptococcus, Pneumococcus, and *H. influenza*. Platelet count, bleeding time, clotting time, prothrombin time, and tourniquet test are normal.

Treatment

A. MEDICAL. Although there are no specifics in the treatment of Henoch-Schönlein syndrome, certain measures appear to be efficacious in reducing the morbidity. Bacterial infections must be vigorously searched for and appropriate antibiotics administered. In long-lasting and recurrent cases elimination of other allergens, such as food, are indicated. Corticosteroids have been widely used to eliminate or minimize the host reaction. Most authors believe that it is efficacious and worthy of trial. The best response to steroids is noted in the edematous swellings of the soft tissues and scalp. The subsidence of gastrointestinal pain and hemorrhage appears to be hastened and it is likely that a reduction in the edematous hemorrhagic areas in the bowel wall may possibly prevent intussusception and massive hemorrhage. The response of the skin and renal lesions to corticosteroid therapy is poor.

B. SURGICAL. Surgical treatment is not usually considered in the vast majority of patients with Henoch-Schönlein purpura even in the presence of abdominal signs and symptoms. Nevertheless two complications require prompt operation—intussusception and perforation; both may occur, the perforation following the intussusception. The occurrence of colicky abdominal pain prior to the onset of the characteristic skin eruption and other manifestations of the disease

presents a puzzling clinical problem to the surgeon. The edematous hemorrhagic lesions in the bowel wall often continue as a lingering process with remissions and exacerbations. Eventually most lesions resolve spontaneously. Sometimes such a lesion serves as the leading point of an intussusception. This is seen most often in males at an average age of six years. Since at this age intussusception is uncommon, when it occurs, anaphylactoid purpura is a good diagnostic possibility.

Lindenauer and Tank reported a study of 50 cases of intussusception complicating Henoch-Schönlein disease in 1966 (2). 72 per cent were children and 28% were older than 17 years of age. 39 operations were performed (2/3 required bowel resection) and five died (13%). 26 operations were performed since 1940 without a mortality. 11 patients were treated without operation and 5 died (55%). One patient with a perforation which was operated upon is the fifth in the literature and the first to survive. These authors emphasize the value of abdominal exploration in doubtful cases in order to avoid the necessity for bowel resection when the diagnosis is delayed. Intussusception is suspected if vomiting is persistent, stools are bloody, or if there is obstipation with marked abdominal distention. Surgery is also considered if the clinical status of the patient appears to deteriorate or where there is continu-

ing doubt concerning the underlying pathology. In the latter instance, the mortality is no greater than that which occurs after exploratory laparotomy in a patient without Henoch-Schönlein purpura. A barium enema often helps to clarify the diagnosis in doubtful cases.

Summary

The salient features and surgical aspects of Henoch-Schönlein purpura are presented.

Older children are apt to have more serious renal lesions which may persist and gastrointestinal lesions (intussusception, perforation) which require surgical treatment.

Abdominal symptoms of pain, vomiting, and intestinal bleeding which occur before the characteristic skin rash present a difficult problem in diagnosis and treatment. The large majority of such patients subside spontaneously. Criteria for operation under such circumstances are outlined.

Julius J. Leichtling

References

1. Allen, D. M., Diamond, L. K., and Howell, D. A.: Anaphylactoid Purpura in Children (Schönlein-Henoch Syndrome), *AMA J Dis Child* 99:833, 1960.
2. Lindenauer, S. M., and Tank, E. S.: Surgical Aspects of Henoch-Schönlein's Purpura, *Surgery* 59:982, 1966.
3. Teplick, J. G., Haskin, M. E., and Schimert, A. P.: *Roentgenologic Diagnosis*, Philadelphia, W. B. Saunders Co., 1967.

Received for publication September 2, 1968

Studies in Bullous Diseases: Treatment of Pemphigus Vulgaris with Methotrexate, Two Patients (One with Concurrent Myasthenia Gravis)

SAMUEL M. PECK, M.D., AND KERMIT E. OSSERMAN, M.D.

Prior to introduction of steroids for treatment of pemphigus vulgaris, mortality rate in this disease was approximately ninety percent. Use of corticoids has markedly reduced this death rate so that in our experience it was well below ten percent. It must be borne in mind that in some instances, steroid therapy itself contributed to mortality. Such incidents were more frequent in the early use of corticoids, especially cortisone where side effects of a serious nature were more evident than with newer analogues.

Since corticoids must be administered for years in most cases of pemphigus vulgaris (some in our series have been followed for over seven years) complications of chronic steroid administration have been encountered. Serious complications have been hyperglycemia, hypertension, and osteoporosis (in some instances leading to pathologic fractures with collapse of vertebrae, for example). Secondary infections, acneiform lesions, moonfacies, hypertrichosis, Cushing's syndrome, muscle atrophy, peptic ulcers, venous thrombosis, hemorrhage, and cataract formation were also seen.

This study is a report of the use of methotrexate in two cases of pemphigus vulgaris, one of whom also has myasthenia gravis. In both cases decision to use methotrexate was influenced by complications of steroid therapy which was given in high doses for long periods of time for control of the disease.

Role of Immunofluorescence Techniques

Introduction of indirect immunofluorescence techniques has not only proved to be of value in diagnosis of pemphigus vulgaris, but serial antiepithelial antibody determinations have proved to be of clinical importance as a guide to management of corticoid therapy (1-5). There is definite relationship between clinical activity and level of antiepithelial antibodies. Dosage of corticoids could often be decreased much sooner because of the drop in antibody titres, which could serve as a predictive guide in imminent improvement and good response to therapy. Conversely, patients on low maintenance dosage who may exhibit few lesions but show a rising titre of antibodies, could be given increased amounts of corticoids in an effort to abort flair-up of the disease (5). Demonstration of autoantibodies against epithelial cells by Beutner and his associates and confirmed by other authors has stressed that pemphigus vulgaris is an autoimmune disease (1-5). This led to trial of immunosuppressive agents

From the Departments of Dermatology, Medicine and Myasthenia Gravis Research Laboratory of Mount Sinai School of Medicine of the City University of New York, New York City, New York.

Supported by The Russ Togs Foundation, Inc.

in treatment of pemphigus vulgaris, especially in those cases where substitute therapy for corticoids would be of great benefit to the patient.

To date, the only immunosuppressive drug used for pemphigus vulgaris is azathioprine (Immunan®). Otto Bier from Brazil has reported its use in the treatment of Brazilian pemphigus. He found that azathioprine administered alone was not successful but used in combination with corticoids, dosage of the latter could be reduced and clinical effect was better than with the use of either drug alone. In our hospital three patients with myasthenia gravis, another autoimmune disease (6), were treated with azathioprine with only partial improvement in one. Another case of myasthenia gravis with inoperable thymoma and metastasis has been improved by treatment with cyclophosphamide (Cytosan®) and vincristine sulfate (Oncovin®). Metastasis has receded and myasthenic symptomatology markedly improved.

Basis for Use of Methotrexate

Methotrexate (4-amino-N₁₀ methyl pteroylglutamic acid) was introduced for treatment of uterine choriocarcinoma and for palliation of acute and subacute leukemias especially in children. Because of its cytotoxic action (reduction of the rate of mitosis in epidermal cells) it has received acceptance by the dermatologist for treatment of widespread resistant psoriasis (7-11). One of us has treated over a hundred cases of psoriasis with methotrexate. The drug can be given orally or parenterally. Since this is a potent medication, contraindications to its use as well as its side effects, which often appear with little warning, must be thoroughly understood. Therapy using this drug is contraindicated in existing hepatic, renal, or bone-marrow damage. Methotrexate has a depressing effect on the hematopoietic system. Certain precautions must be taken such as frequent blood counts and monthly liver function studies. Most frequent side effects are those affecting white blood cells, platelets, hemoglobin, and liver functions. It has recently been stressed that there may be danger of liver toxicity when methotrexate is given in relatively high dosages over long periods of time (12). Also encountered are gingivitis, pharyngitis, stomatitis, occasional toxic eruption, gastrointestinal irritation (including silent perforations), nausea, vomiting, and diarrhea. Another annoying minor effect is headache which can be controlled by lowering dosage. Administration of this drug *must* be discontinued when the white blood cell count falls to 3,000 or less; or when platelets fall to 90,000.

Case Reports

CASE I

A 32-year-old white woman with a well-documented case of myasthenia gravis and concomitant pemphigus vulgaris, has had several biopsies demonstrating classic changes with acantholysis (5). She has been observed at 7 to 10 day intervals since 1964. At times she had many bullous lesions both on buccal mucosa and scattered areas of the body. When first seen these lesions were easily controlled by steroids. During hospital admissions and the greater period of clinical observations, a minimum of 16 mg of methylprednisolone daily and 60 to 120 units of zinc adrenocorticotrophic hormone (ACTH) weekly was

required in order to keep the pemphigus vulgaris under control. The myasthenia gravis was treated with pyridostigmine bromide (Mestinon®). She experienced many side effects from steroids including a marked acneiform eruption with a pustular element that was constantly present. Most serious complication of steroid administration was development of deltoid and quadriceps atrophy and absorption of alveolar processes of teeth and evidence of osteoporosis in long bones. She was very prone to secondary infection and had to be hospitalized on a number of occasions because of severe urinary infection. At one time a kidney stone developed which required surgery. Some acneiform eruptions were thought to be accounted for by finding of an increased blood bromide level of 44 mg%, possibly due to the bromide radical present in pyridostigmine. Substitution of pyridostigmine chloride only partly relieved acneiform eruption. She experienced hypertrichosis, moonfacies, and a tendency to bleed with marked purpuric eruptions. Slight trauma caused separation of upper layers of skin which necessitated suturing on a number of occasions. There was water retention, which was brought under control from time to time with diuretics. Electrolytes were within normal range.

In May 1968, in order to maintain her relatively symptom-free from pemphigus vulgaris, she required larger daily doses of methylprednisolone (24 mg) and greater doses of zinc ACTH (180 units weekly in three divided doses). Despite this high dosage, antiepitheial titre was 1:80. Adjustments in corticoids required changes in pyridostigmine chloride dosage in order to control symptomatology of myasthenia gravis. Because of previous adverse side effects with increasing doses of corticoids it was decided to begin the use of methotrexate.

Figure 1 demonstrates that administration of methotrexate in dosages of 25 mg intramuscularly in divided doses of 12.5 mg twice a week, caused a consistent drop in anti-

PEMPHIGUS VULGARIS

CORRELATION OF CLINICAL ACTIVITY WITH ANTIBODY TITER & THERAPY

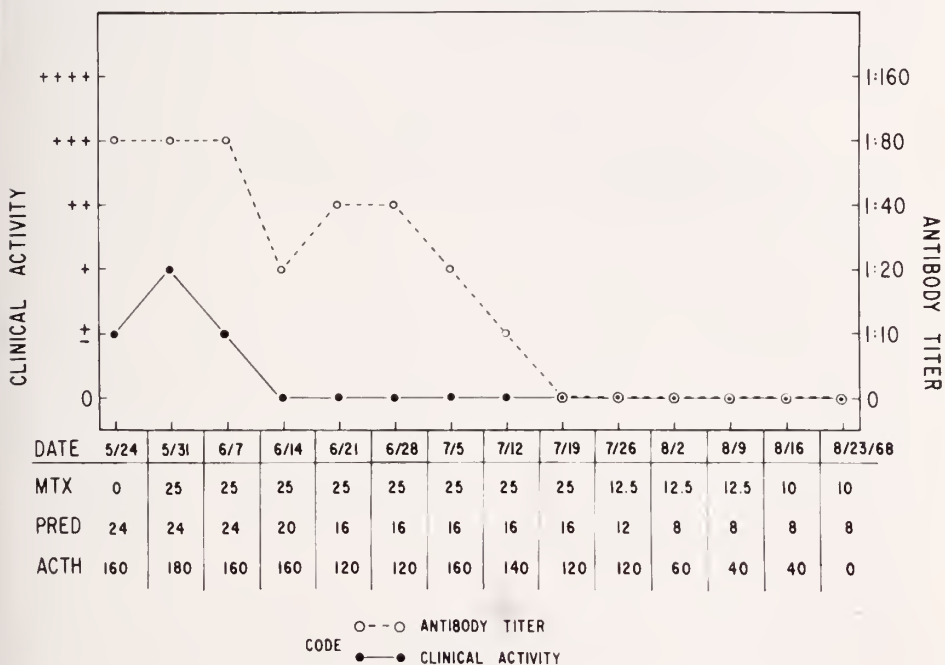


Fig. 1. Pemphigus vulgaris and myasthenia gravis.

epithelial antibody titre. Steroids were gradually reduced. By August 23, 1968, ACTH had been discontinued, methylprednisolone reduced to 8 mg a day and methotrexate has been lowered to 10 mg a week intramuscularly. The blood count never presented a problem. There were no adverse effects on white blood count which varied from 10,000 to 4,750, hemoglobin, platelet count, or liver functions. The myasthenia gravis and pemphigus vulgaris are currently in remission, which had never been achieved during her four years of treatment with corticoids alone. Some secondary effects of corticoids such as acneiform eruptions, water retention, and moonfacies have been markedly decreased. The anti-epithelial antibody titre remains negative the past month.

Assessment of clinical activity in this study as shown in figures 1 and 2:

(1) 2+ to 4+ activity; a patient with extensive bullous lesions on the body but not necessarily on the buccal mucosa.

(2) 1+ to \pm activity; a patient with relatively few lesions on the body with only occasional lesions on the buccal mucosa.

(3) "0" activity; a patient without any clinical symptoms and usually seen when disease is in remission.

CASE 2

A negro woman, aged 56 with several Mount Sinai Hospital admissions, was born in the Virgin Islands and had had pemphigus vulgaris for six years. When readmitted to the hospital March 1968, she had bullous lesions on neck, face, and extremities. Diagnosis was based on clinical appearance and histologic examination which was typical for pemphigus vulgaris with acantholysis. At this admission she required 40 mg of prednisone daily which did not control the disease, anti-epithelial titre was 1:160. On physical examination found were moderate hypertension, tachycardia with extra systoles, dyspnea on exertion, bladder infection, and joint pains. Because this patient would require increased amounts of steroids for control of her bullous lesions and was already exhibiting steroid toxicity in the form of spinal osteoporosis, hyperglycemia, decreased resistance to infection and increased ocular tension; attempts were made to limit use of steroids by adding methotrexate to therapy.

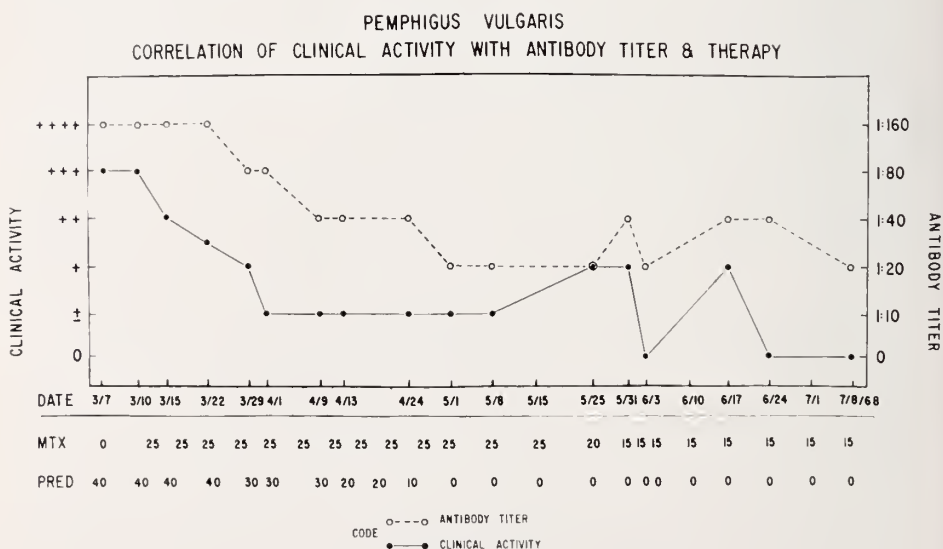


Fig. 2.

Figure 2 illustrates clinical course and antibody titres when methotrexate was started in March 1968. The patient was discharged on June 7, 1968 and has been followed weekly in the out-patient department. White blood count determinations fluctuated between 13,500 and 5,000; platelets were adequate and no evidence of liver damage. Methotrexate was gradually reduced from an initial weekly administration of 25 mg intramuscularly to 15 mg weekly by May 31, 1968. Steroids were gradually decreased and on May 1, 1968 were discontinued. Except for three tiny body lesions on June 17, 1968, there were no mouth lesions or bullae to be seen on the body from date of discharge until present. Antiepithelial antibody titre has decreased from initial 1:160 level and was generally maintained at a level of 1:20-1:40. On August 28, 1968 she exhibited 1+ clinical activity and antibody titre rose to 1:80 indicating inadequate dosage level of methotrexate.

Discussion

Use of methotrexate appears to be successful in two cases reported, bringing about not only suppression of clinical manifestations but also decrease in antiepithelial antibody titre, which was somewhat delayed after clinical improvement. Immunosuppressive action of this drug on antibody formation brought about the objective of this study which was a decrease or elimination in use of corticoids necessary to keep pemphigus vulgaris under control.

Case 1, pemphigus vulgaris and concomitant myasthenia gravis was followed intensively for over four years. Because of the myasthenia gravis, approach to therapy was a problem since effects of steroids caused muscle atrophy adding to the problem of neuromuscular defect. During the years of study of this case, there were only short periods of time when steroids could be given in minimum doses of 16 mg of methylprednisolone daily. The patient also required zinc ACTH rather than greater doses of cortisone by mouth since this combination of corticoids would have less adverse effect on myasthenia gravis. It was decided to administer an immunosuppressive agent in the form of methotrexate in an attempt to avoid higher doses of corticoids. Figure 1 illustrates success of the therapeutic program.

Case 2, pemphigus vulgaris required high doses of steroids for control. For many years the antiepithelial antibody titre was at a high level of 1:320, indicating the disease was far from being fully controlled even with the amounts of steroids received. Due to the long duration of therapy there were marked corticoid side effects. Figure 2 illustrates clinical improvement with decreased antiepithelial antibody titre permitting discontinuance of steroid administration before patient left hospital. She is now receiving 15 mg of methotrexate intramuscularly weekly. She has tolerated treatment well. Apparently she will require increased amounts of methotrexate and possibly addition of small doses of steroids since she is exhibiting increased levels of antibody titre and recurrence of mild clinical activity.

Another patient with pemphigus vulgaris under treatment with methotrexate seems to be responding well but has not been followed long enough to be included in this report.

In our limited experience it has not yet been determined the most effective dosage schedules, minimum maintenance dose, and relapse rate. Mode of therapeutic action, besides suppression of antiepithelial antibody formation,

needs further study. It may be that for ideal maintenance dosage, a combination of small amounts of methotrexate plus small amounts of steroids may be more practical for minimizing possible side effects of either drug. As yet, opportunity has not presented itself to study use of methotrexate as the only therapeutic agent in an untreated case of pemphigus vulgaris.

Methotrexate (an immunosuppressive agent) was used for treatment of an autoantibody disease in an attempt to suppress antibody formation. This hypothesis seems to be only part of the mechanism since clinical improvement preceded fall of antiepithelial antibody titre. Relief of symptomatology of pemphigus vulgaris was much more rapid with combinations of methotrexate and steroids than steroids alone.

ACKNOWLEDGMENT

The authors are grateful to Miss Ruth Sue Osserman for her statistical analysis.

Generic and trade names of drugs: methotrexate—Methotrexate (Lederle), methylprednisolone—Medrol, azathioprine—Immunar, cyclophosphamide—Cytosan, vincristine sulfate—Oncovin, pyridostigmine bromide—Mestinon.

References

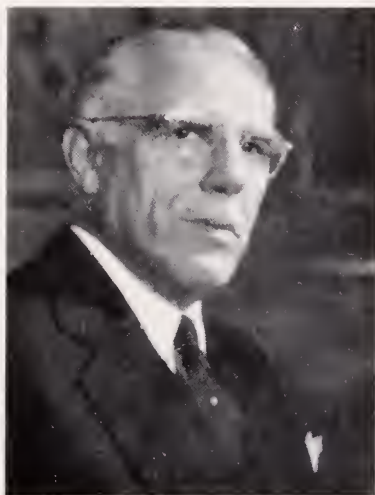
1. Beutner, E. H., and Jordon, R. E.: Demonstration of Skin Antibodies in Sera of Pemphigus Vulgaris Patients by Indirect Immunofluorescent Staining, *Proc Soc Exper Biol & Med* 117:505-10, 1964.
2. Beutner, E. H., Lever, W. F., Witebsky, E., Jordon, R. E., and Chertock, B.: Autoantibodies in Pemphigus Vulgaris. Response to an Intercellular Substance of Epidermis, *JAMA* 192:682-88, 1965.
3. Chorzelski, T. P., von Weiss, J. V., and Lever, W. F.: Clinical Significance of Autoantibodies in Pemphigus, *Arch Derm* 93:570-76, 1966.
4. Chorzelski, T., Jablonska, S., and Blaszczyk, M.: Autoantibodies in Pemphigus, *Acta Dermatovenere Sven Hellerstrom* (65 yrs.), 47:26-33, 1966.
5. Peck, S. M., Osserman, K. E., Weiner, L. B., Lefkowitz, A., and Osserman, R. S.: Studies in Bullous Diseases, *New Eng J Med* 279:951-58, 1968.
6. Strauss, A. J. L., Seegal, B. C., Hsu, K. C., Burkholder, P. M., Nastuk, W. K., and Osserman, K. E.: Immunofluorescence Demonstration of a Muscle Binding, Complement-fixing Serum of Globulin Fraction in Myasthenia Gravis, *Proc Soc Exper Biol & Med* 105:184-191, 1960.
7. Auerbach, R.: Parenteral vs Oral Folic Acid Antagonist, *Arch Dermat Chicago* 90:553-57, 1964.
8. Black, R. L., et al: Therapy in Psoriatic Arthritis, *JAMA* 189:743-47, 1964.
9. Scott, E. J. Van, Auerbach, R., and Weinstein, G. D.: Parenteral Methotrexate in Psoriasis, *Arch Dermat Chicago* 89:550-56, 1964.
10. Wright, E. T., Worborsky, M., and Hamer, E.: Human Low-dosage Parenteral Methotrexate Therapy, *Arch Dermat Chicago* 93:731-36, 1966.
11. Frank, L., Lechtman, H., Biro, L., and Petrou, P.: Experiences with Methotrexate in Psoriasis, *Dermatologica* 137:87-96, 1968.
12. Coe, R. O., and Bull, F. E.: Cirrhosis Associated with Methotrexate Treatment of Psoriasis, *JAMA* 206:1515-20, 1968.

Received for publication November 26, 1968

ANNOUNCEMENT

THE RALPH COLP AWARD FOR 1966

Dr. Mahmood A. Naqvi is the recipient of the Ralph Colp Award for 1968, for his paper, "Intraperitoneal Hemorrhage as a Complication of Acute Ruptured Cholecystitis," co-authored with Dr. Callisto A. Danese and Dr. David A. Dreiling.



This award is made by the Ralph Colp Fund, for the best paper published in the Journal of The Mount Sinai Hospital by a member of the house staff or a junior member of the attending staff. Preference is given to papers on surgical subjects. The Fund was established in honor of Dr. Ralph Colp, distinguished surgeon and long-time Chief of Surgery at The Mount Sinai Hospital.

THE DANIEL STATS MEMORIAL PRIZE FOR 1968

The Dr. Daniel Stats Memorial Committee is pleased to announce that Dr. Carlos Dominguez, formerly of the Department of Hematology, The Mount Sinai Hospital, New York, N. Y. is the recipient of the Daniel Stats Memorial Prize for 1968. His paper, entitled "Antigenic Heterogeneity of Reduced and Alkylated Subunits of Human Monoclonal Macroglobulins" was unanimously chosen by all the reviewers. Dr. Dominguez has recently completed two years as Senior Cancer Clinical Trainee in Hematology.

The Daniel Stats Prize is in the sum of \$150 and the competition is open to all members of the House Staff as well as Hospital Fellows.

MOUNT SINAI SCHOOL OF MEDICINE OF THE

CITY UNIVERSITY OF NEW YORK

THE PAGE AND WILLIAM BLACK
POST-GRADUATE SCHOOL OF MEDICINE

ANNOUNCES ITS POST-GRADUATE COURSES FOR
JANUARY-JUNE, 1969

COURSES FOR GENERAL PRACTITIONERS

Care of the Stroke Patient* Lawrence H. Wisham, M.D., Lawrence I. Kaplan, M.D. and Associates.	Winter and Spring 1969, Dates and hours to be announced.
Clinical Chest Diseases Louis E. Siltzbach, M.D. and Associates	January 2 to March 6, 1969, Thursdays, 4:00 PM to 5:30 PM.
Laboratory Methods in Hematology Louis R. Wasserman, M.D., and Associates.	January 27 to January 31, 1969, Monday through Friday, 9:00 AM to 5:00 PM.
Dermatology in General Practice Samuel M. Peck, M.D. and Associates.	March 3 to March 24, 1969, Mondays and Thursdays, 9:00 AM to 10:00 AM.
Hypnosis for the Physician and Dentist Elliot N. Wineburg, M.D.	March 6 to May 22, 1969, Thursdays, 4:30 PM to 6:00 PM.
Recent Developments in Obstetrics and Gynecology Saul B. Gusberg, M.D. and Associates.	March 13, 14 and 15, 1969, Thursday and Friday, 9:00 AM to 5:00 PM, Saturday, 9:00 AM to 12 Noon.
Laboratory Methods in Blood Banks Richard E. Rosenfield, M.D. and Associates.	March 17 to March 19, 1969, Monday through Wednesday, 9:00 AM to 5:00 PM.
Clinical Neurology Morris B. Bender, M.D. and Associates.	March 17 to March 21, 1969, Monday through Friday, 9:00 AM to 5:00 PM.
Differential Diagnosis in Gastrointestinal Radiology Richard H. Marshak, M.D. and Man-sho T. Khilnani, M.D.	March 18 to May 20, 1969, Tuesdays, 5:00 PM to 6:00 PM.
Gastroenterology Henry D. Janowitz, M.D. and Associates.	March 24 to March 28, 1969, Monday through Friday, 9:00 AM to 5:00 PM.
Differential Diagnosis in Radiology of the Chest Coleman B. Rabin, M.D. and Bernard S. Wolf, M.D.	March 24 to June 9, 1969, Mondays, 5:00 PM to 6:00 PM.
Home and Office Care of Peripheral Vascular Disease and Its Sequelae Including Amputation* Lawrence H. Wisham, M.D., Lawrence I. Kaplan, M.D. and Associates.	Spring 1969, Dates and hours to be announced.
Prevention and Treatment of Disability in Most Common Types of Arthritis* Lawrence H. Wisham, M.D., Lawrence I. Kaplan, M.D. and Associates.	Spring 1969, Dates and hours to be announced.
Rehabilitation of an Arthritic Lawrence Wisham, M.D., Frances Dworecka, M.D. and Associates.	April 16, 1969, Wednesday, 9:00 AM to 1:00 PM.
Annual Teaching Conference on Arthritis Selvan Davison, M.D., Frances Dworecka, M.D. and Associates.	May 21, 1969, Wednesday, 9:00 AM to 1:00 PM.

* To be held at the City Hospital Center at Elmhurst, New York.

Current Therapy of Cystinuria

HOWARD J. GOLDMAN, M.D. AND STANLEY I. GLICKMAN, M.D.

Cystinuria is a complex hereditary metabolic disorder involving both the gastrointestinal tract as well as the renal tubule. Its solitary clinical manifestation appears to be limited to recurrent formation of cystine calculi despite the fact that the metabolic abnormality involves all of the diamino-amino acids—cystine, arginine, lysine, and ornithine—as well as possibly cysteine.

Prior to 1963 the prevention of recurrent calculi was often unsuccessful despite vigorous prophylactic therapy, i.e. maintenance of excessively large fluid intake, alkalization of the urine, and dietary restrictions. Numerous surgical and cystoscopic procedures were often necessary to preserve renal function and to relieve acute blockades of the urinary tract. The whole concept of therapy and the prognosis of this disease were radically changed with the introduction by Crawhall (1) in 1963 of the use of oral penicillamine to decrease the insoluble cystine in the urine. Recent developments, however, have cast some doubt on the advisability of using this medication routinely on all cystinurias and prompts this review of our experience over the past five years.

Apart from this tendency to recurrent calculus formation, these patients remain remarkably well, exhibiting no nutritional or constitutional abnormalities.

The primary cause of stone formation is the high urinary concentration of cystine—the least soluble of the amino acids in an acid urine. Most cystinuric patients excrete in excess of 300 mg of cystine per day. At a pH of 5 Dent and Senior (2) have shown that 250 mg of cystine are held in a liter solution while at a pH of 7 this increases to 400 mg, rising up to 1 gm/liter at a pH of 8.

Lysine, arginine, and ornithine are freely soluble and do not cause calculi or precipitate on the cystine nidus.

The hypothesized renal defect is a transport abnormality in the proximal renal tubule preventing the resorption of the diamino-amino acids from the glomerular filtrate, allowing their excretion in excess amounts in the urine. This theory conjectured that amino acids having a common structure with two amino groups separated by four to six atoms shared a common pathway for renal tubular resorption. The results of numerous studies through the mid 1950's appeared to substantiate this theory, but recent sophisticated techniques, not previously available, have cast great doubt upon the validity of this assumption.

An alternative hypothesis has been proposed which states that cysteine, not cystine, shares a transport mechanism with lysine, ornithine and arginine;

From Department of Urology, the Mount Sinai School of Medicine, New York, New York.

that this mechanism is defective in cystinuria; and that the elevated urinary cystine content results from dimerization of two cysteine molecules in the tubular urine or renal pelvis (3).

Case Reports

CASE 1. N.S., a 22-year-old white girl was first admitted to The Mount Sinai Hospital on December 7, 1957 with a six day history of left flank pain and abdominal distension. The preliminary film of the excretory pyelogram revealed two large, lightly opaque, calculi over the course of the lower right ureter with no opaque stones evident over the left urinary tract. There was no excretion of contrast medium from the left kidney after one hour and a moderate right uretero-hydronephrosis was present. Cystoscopy and left ureteral catheterization were performed on the day of her admission to the hospital. The ureteral catheters were left indwelling for three days and upon their removal she passed a small calculus. A right uretero-lithotomy with removal of two stones was then performed with an uneventful outcome.

Chemical analysis of the stones removed was reported as "containing no usual constituents of renal calculi." Her urine was persistently acid and her blood uric acid was 5.0 and 7.1 mg% on two occasions. A large fluid intake and alkalinization of her urine were recommended.

She was readmitted on November 5, 1958 with a one week history of left renal colic. A left uretero-lithotomy was performed for a large, lightly opaque, calculus which was impacted a few centimeters beyond the uretero-pelvic junction. Chemical analysis of the stone revealed pure cystine. She was placed on a low protein diet in conjunction with a large fluid intake and alkalinization of her urine.

In November of 1960 she had an attack of left renal colic and passed a pea-sized stone. An x-ray in May 1961 revealed no stones on the right side but a large, lightly opaque calculus was present in the lower left calyx. In June 1961 a small calculus blocked the upper left ureter. Left ureteral catheterization temporarily unblocked the kidney, but after removal of the ureteral catheters severe pain recurred requiring a left uretero-pyelolithotomy with removal of two stones.

In March of 1962 a bean-sized stone was noted in the lower pole of the left kidney. The stone continued to grow in size and on October 20, 1963 she was started on 1.5 gm of D-penicillamine daily, in four divided doses. The 24 hour urinary excretion of cystine was 805 and 900 mg on the two days prior to therapy, falling to a level of 250 mg after three days of penicillamine administration.

On October 27, 1963, seven days after starting medication, a reddish maculo-papular eruption developed on the upper half of her body, greatest in intensity around her neck. This was associated with severe nausea and temperature of 103°. She was started on oral anti-histamine while continuing the same dosage of penicillamine. The rash and fever completely disappeared within 48 hours while the pruritis persisted for about a week.

On November 4, 1963, she stopped taking penicillamine because of severe nausea. She had become nauseated at the inception of the drug regime despite the use of antacids and the ingestion of the pills after meals.

On January 6, 1964 her 24 hour urinary cystine excretion was 575 mg. On January 9, 1964 she restarted a course of D-penicillamine with a reduced dosage schedule of 0.75 gm a day and her urinary levels promptly fell to about 200 mg a day.

This dosage (750 mg a day) was continued despite a constant sensation of nausea until May 11, 1964 at which time a left nephrolithotomy was performed, inasmuch as there had been a slow increase in the size of her stone despite therapy. An excretory pyelogram at this time revealed no stones in either kidney.

Her 24 hour excretion of cystine at the time of surgery had risen to 750 mg a day after having had no medication for two days, but it promptly fell to the range of 250 mg on the resumption of the drug. She has been taking D-penicillamine continuously

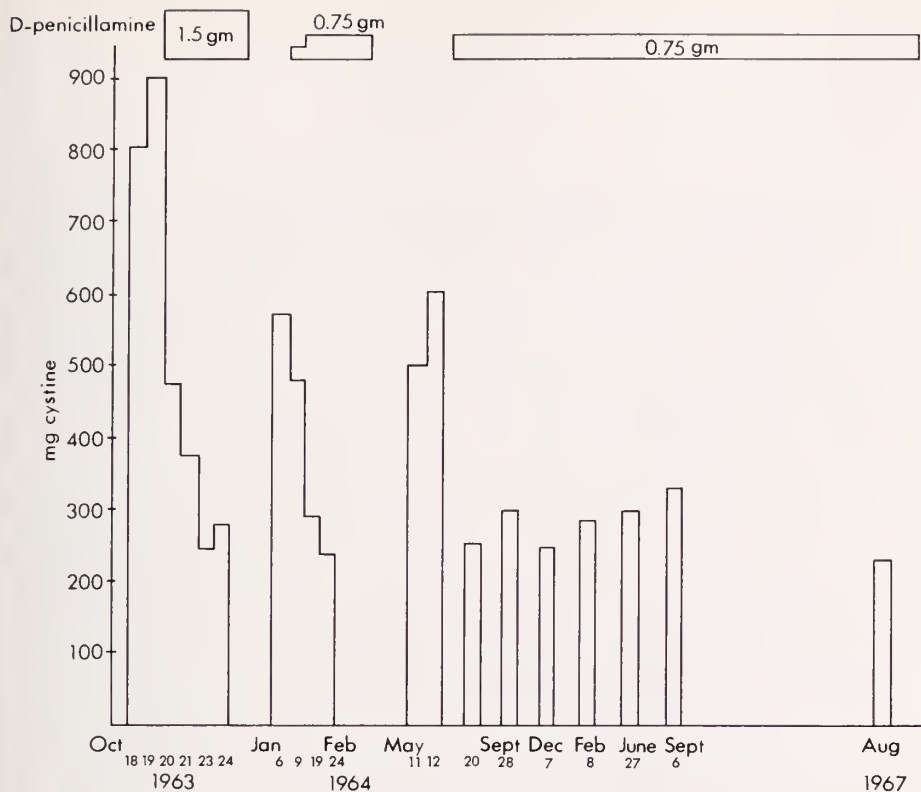


FIG. 1. Cystine excretion in Case 1, NS.

since 1964, taking either 750 mg or 1 gm daily, in three or four-divided doses, with no adverse effects other than minimal nausea, which she has learned to tolerate. Twenty-four hour urinary excretion studies of cystine were 230 mg in December 1964, 260 mg in February 1965, and 170 mg in August 1967. (See Fig. 1) An excretory pyelogram taken on May 3, 1965 revealed excellent function bilaterally with no evidence of calculi. She has been taking 25 mg of pyridoxine daily, along with a large fluid intake and she has noted that her urine pH is often in the range of 7 without any alkali ingestion. Prior to taking D-penicillamine, despite the ingestion of large doses of alkali, her urine pH was difficult to raise above 5.5 or 6.0.

There were no definite calculi noted on an x-ray taken in February 1968. Her urine was negative on microscopic examination and no proteinuria was present.

CASE 2. E.P. at the age of 15 experienced a severe attack of left flank pain of one day's duration. A year later he again experienced left flank pain at which time an excretory pyelogram revealed a normal appearing left kidney but a markedly hydronephrotic and poorly functioning right kidney. No definite stones were seen. In June 1939 he underwent a right nephrectomy for removal of a pyonephrotic kidney which contained a large dendritic stone as well as twenty smaller stones. Chemical analysis of all of these revealed cystine.

He was placed on sodium bicarbonate to alkalinize his urine but despite this, passed six small stones over the next six years. In 1945 he was admitted to The Mount Sinai Hospital in an anuric state. He underwent two cystoscopic manipulations after which he passed fifteen small stones.

In 1946 and 1947 he again required left ureteral catheterization to relieve anuria.

TABLE I
Cystine and Uric Acid Levels in Case 2, (EP)

Date	Serum Uric Acid (mg%)	Cystine (mg/24 hrs.)
2/3/66		1080
5/10/66	8.6	1095
6/27/66	8.9	580
8/12/66	7.9	635
11/18/66	8.8	880
2/21/67	10.0	500
5/23/67	9.1	600
7/25/67	9.3	600
10/17/67	10.2	568
1/9/68	7.9	714
2/27/68	8.9	—

In 1947 he underwent two separate left uretero-pyelolithotomies for large stones impacted in the upper ureter. He continued to alkalinize his urine and maintain an intake of at least two quarts of fluid a day but occasionally had a severe colic and passed a small stone.

For a period of five years from 1960 through 1964 he was totally asymptomatic despite no use of sodium bicarbonate.

In June 1964 and January 1966 he underwent emergency cystoscopic procedures for anuria. Over this two-year period he had passed numerous small calculi.

On February 3, 1966 a 24 hour urinary excretion of cystine was 1080 mg on an regular hospital diet. On May 10, 1966 a second control was 1095 mg. He was started on 1.5 gm of D-penicillamine daily in divided doses on May 13, 1966. On May 20, 1966 (one week after starting medication) his temperature spiked to 102° and a red macular rash developed over his entire body. The daily dosage of penicillamine was reduced by half and he was treated with anti-histamine. His temperature returned to normal after 48 hours but the rash and pruritus persisted for another week. At that time the dosage was raised to 1.5 gm a day. On June 27, 1966 the 24 hour excretion of cystine was 580 mg. He has remained on this medication over the past 20 months and has not experienced a colic or passed any stones. He is taking 25 mg of pyridoxine daily but has not taken any alkali. Excretory pyelograms in January 1967 and March 1968 revealed no calculi. His 24 hour urine excretions of cystine on penicillamine have varied between 500 and 800 mg (Table I). His blood uric acids have been persistently elevated—varying between 7.9 and 10 mg (Table I).

CASE 3. H.G. had a negative urological history until the age of 22 at which time she experienced a mild urinary tract infection. An excretory pyelogram demonstrated a large calculus occupying the pelvis and calyces of the left kidney. The kidney visualized poorly with the typical radiographic changes of pyelonephritis evident in all the calyces. The right urinary tract was perfectly normal. Her past medical history was unremarkable except for an appendiceal abscess the previous year.

She underwent a left nephrectomy in September 1949. The gross and microscopic examination of the kidney revealed a calculus pyelonephritis. Chemical analysis of the stone was cystine.

She remained asymptomatic through three pregnancies in 1953, 1954, and 1956 but in November 1954 passed a triangular stone which had impacted in her lower right ureter.

A routine pyelogram in May 1966 revealed a small calculus in the upper pole of her right kidney (Fig. 2). The calculus was in a calyx and measured about one centimeter in diameter. A 24 hour urine collection revealed 990 mg of cystine.

On June 25, 1966 she was started on two grams of D-penicillamine (Cuprimine) daily in four divided doses as well as 25 mg of pyridoxine daily. An x-ray on August 17, 1966 (Fig. 3) revealed a definite diminution in the size of the stone. An x-ray on November 29, 1966 (Fig. 4) revealed no evidence of the right renal calculus. A repeat excretory pyelogram on January 24, 1967 (Fig. 5) confirmed the absence of the stone and its ap-



FIG. 2a. Case 3, May 1966, demonstrating right calyceal calculi.



FIG. 2b. Case 3, May 1966, demonstrating right calyceal calculi.

parent complete resolution. A 24 hour urine collection in November 1966 (while continuing on two grams of D-penicillamine daily) revealed 261 mg of cystine and 858 mg of penicillamine—cystine mixed disulfide.

She has continued to take two grams of D-penicillamine daily and has remained asymptomatic.

CASE 4. D.B. This patient was asymptomatic until the age of 14 years, at which time he experienced an attack of right renal colic and passed a small stone. He was x-rayed and cystoscoped but no abnormality was found. Over the next six years he experienced many attacks of both left and right renal colic, passing about 25 stones. In 1955 an excretory pyelogram revealed one large and five small, lightly opaque, calculi in the right kidney and one small calculus in the left kidney. No hydronephrosis was present on either side. The physical examination was unremarkable. His father had once passed a kidney stone but there was no other familial history of calculus disease.

On March 24, 1955 he experienced severe right flank pain and an excretory pyelogram revealed the large right renal calculus to have descended to the upper ureter, opposite the transverse process of the third lumbar vertebra, with a small stone lying just above it. An emergency right ureterolithotomy was performed with removal of these two stones, which were composed of pure cystine.

Although he was placed on a low protein diet, along with alkalinization of his urine, and he faithfully increased his fluid intake to two quarts a day, he continued to pass many stones.

On January 27, 1960 a large stone was surgically removed from the upper left ureter. On January 3, 1963 a high right ureterolithotomy was performed. He had been adhering to the "Mayo Clinic low purine diet," and following the other precepts, but he continued to pass many stones. On January 31, 1966 he underwent an emergency left uretero-pyelolithotomy for a blocked kidney due to a large stone impacted one centimeter below the pelvis. Following recuperation from surgery the patient agreed to start D-penicillamine,



FIG. 3. Case 3, August 1966, demonstrating diminution in size of calyceal calculi under D-penicillamine therapy.

which he had refused to take previously. An excretory pyelogram revealed prompt bilateral renal function with no calculi noted at this time.

On December 20, 1965 a 24 hour urine on a low purine diet revealed 948 mg of cystine. On February 10, 1966 on a regular hospital diet it was 946 mg. On April 18, 1966, after taking 1.5 gm of D-penicillamine daily for 6 weeks, his 24 hour urinary cystine excretion was 338 mg (Fig. 6). He tolerated the medication well except for transient itching of his arms. Repeated blood counts and liver function tests were normal.

In October 1966 he passed a small stone and his dosage was increased to two grams

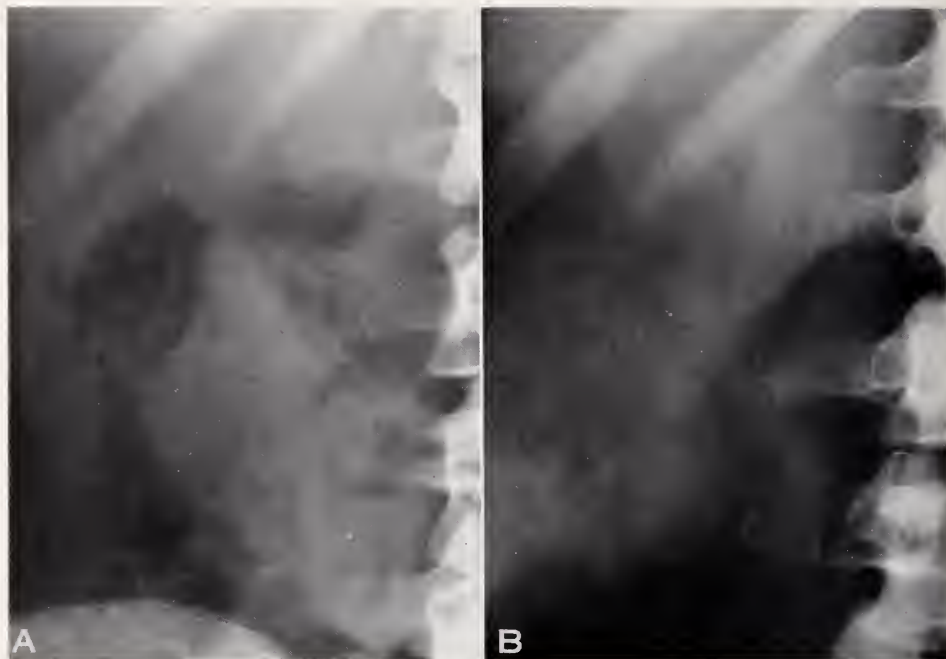


FIG. 4. Case 3, November 1966, revealed no stone evident. a) A-P view. b) Right oblique view.

daily. On February 9, 1967 his 24 hour cystine excretion was 214 mg. An x-ray in October 1967 failed to disclose any definite calculi.

A routine urine on October 15, 1967 revealed 4+ albuminuria with no cells or casts noted. On October 23, 1967 the following blood studies were performed: total protein 7.5 gm%, albumin 4.1 gm%, alpha globulin 0.3 gm%, alpha 2 globulin 0.95 gm%, beta globulin 0.87 gm%, gamma globulin 1.30 gm%, serum cholesterol 278 mg%. Quantitative urinary protein revealed 1.3 gm/liter with an out-put of 2.5 liters (3250 mg per 24 hours).

Penicillamine was stopped on October 20, 1967. On November 1, 3+ albumin was present, November 24, a trace and on December 8 no albumin was present (see Table II). On November 27 he passed a small stone. On December 8 he was started on 10 mg of prednisone daily and three days later, one gram of penicillamine daily. On December 11, 1+ albumin was present but by December 29, 3+ albumin was present. The 24 hour urinary protein was 980 mg. Penicillamine was again discontinued and prednisone was tapered off. On January 6, 1968 he had left renal colic and passed a small stone. On January 12, 1968, one gram of penicillamine was restarted with no steroid coverage. Repeated urine determinations have revealed between 1 and 2+ albuminuria with 24 hour excretion levels between 290 and 997 mg (Table II).

Daily levels of proteinuria have averaged 500 mg/24 hrs through January 1969. He received one gram of penicillamine daily through June 1968 but passed a few small cystine stones. The dosage was increased to two grams per day with no increase in proteinuria and no further passage of stones. No renal abnormalities except the proteinuria have since developed.

Discussion

Therapy prior to the introduction of penicillamine was directed towards three areas: a low methionine diet, increasing the urinary output and alkalmi-



FIG. 5. Case 3, January 1967, confirmed absence of calyceal calculi.

zation of the urine. The rationale of a low methionine diet is that this sulfur compound is the major precursor of cystine. The restriction of dietary methionine to one gram a day can be accomplished by limiting the animal protein intake to 0.5 mg/kg/day (4).

Protein can then be supplemented by the addition of peanut butter. Despite careful control of urinary volume and alkalinity, this low sulfur diet has been found to be ineffective for the first 4 to 6 weeks. However, subsequent to this there was diminution in cystine excretion in all patients studied, with a drop of 25% in some cases (5). Most patients with cystinuria refuse to adhere to this unpalatable diet which is accepted only by those few who have undergone numerous operations for removal of stones.

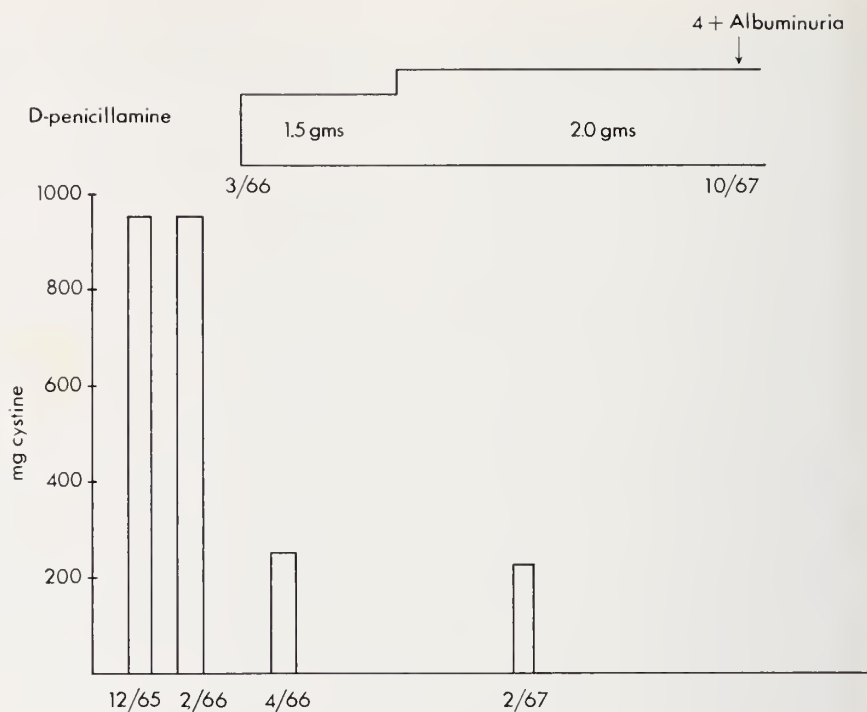


FIG. 6. Cystine excretion in Case 4, DB.

Other investigators have failed to verify any influence on cystine excretion either by restricting or administering dietary methionine (6, 7).

It is also difficult to obtain patient acceptance of the second aspect of therapy—adequate fluid intake. Dent was unable to maintain one-third of his patients on such a regime despite a forceful educational program. A urinary volume of 2 cc per minute, throughout a 24 hour period is necessary to maintain the urinary specific gravity at or below 1.010. This necessitates drinking one pint every four hours and requires waking once at night. Of eighteen of Dent's patients following only this regime (no diet or alkalinization of urine) twelve were able to maintain it for over four years. Of the six that were stone free at the outset, none had recurrences. Three had marked dissolution of calculi and the remaining three had some dissolution (2, 7).

The third aspect of therapy is alkalinization of the urine which can be accomplished by the use of sodium bicarbonate or sodium potassium citrate. As discussed previously, the solubility of cystine rapidly increases with increasing alkalinity and a pH between 7.0 and 7.5 is usually recommended. A higher pH than 7.5 is undesirable to avoid systemic alkalosis, nephrocalcinosis or deposition of calcium on existing cystine stones. Dent (7) is of the opinion that the customary dosage of alkali therapy has no real value in the therapy of cystinuria and that only a very high dosage (30 gm of bicarbonate a day) can ensure a constant pH of 7.5. He concurs in the dangers of maintaining this

TABLE 11

Case 4, (DB) Relationship of Albuminuria and D-penicillamine Administration in Nephrotic Syndrome

Date	Penicillamine (gms./24 hrs.)	Prednisone	Protein	mg./24 hrs.
10/15/67	2		4+	
10/20/67	Discontinued			
10/23/67	0			3250
11/1/67	0		3+	
11/24/67	0		Trace	
12/8/67	0	10	Negative	
12/11/67	1	10		
12/29/67	Discontinued	Tapered	3+	980
1/12/68	1		2+	660
1/15/68	1		1+	291
1/19/68	1		2+	997
1/22/68	1		1+	630
1/26/68	1		2+	828
1/29/68	1		1+	348
4/1/68	1			474

pH and reserves it for patients who cannot follow a regime of large fluid intake.

Treatment with D-Penicillamine

J. C. Crawhall and associates (1) in 1963 reported on the successful use of this compound in reducing the concentration of urinary cystine by the formation of a mixed disulfide which had a much greater solubility in the urine than cystine. D-penicillamine had previously been used successfully as a chelating agent in Wilson's disease since 1956 (8) and in lead poisoning.

Penicillamine and cysteine represent the free sulfhydryl forms of amino acid. They readily convert to the disulfide form, by loss of the sulfur proton and linking of two molecules by one disulfide bond, penicillamine forming penicillamine disulfide and cysteine forming cystine (see Fig. 7).

In a similar manner, penicillamine may react with cystine, through a disulfide interchange, with linking of two dissimilar amino acids by a common disulfide bond. This compound, penicillamine-cysteine mixed disulfide has been found to be 50 times more soluble than cystine.

In their first report in 1963, Crawhall et al (1) reported on the use of D-penicillamine on two cystinuric patients. The cystine excretion was abolished or reduced according to the dosage of penicillamine used. During penicillamine administration two new substances appeared in the urine which on chromatographic examination were found to be penicillamine-cysteine disulfide and penicillamine disulfide. Solubility studies of these compounds were found to be 50 and 500 times that of cystine, respectively (9).

Numerous studies over the past five years have confirmed these results (3, 9-16). With increasing D-penicillamine dosage there is a progressive

fall in free urinary cystine corresponding with the appearance of penicillamine-cysteine disulfide and penicillamine disulfide. In most cases two gm of D-penicillamine daily, in divided doses, were sufficient to reduce the 24 hour urinary cystine excretion to below 200 mg.

A surprising observation that was constant only in the cystinuric patients was that total cystine excretion (measured as the total cystine present as free cystine plus that present as cysteine in penicillamine-cysteine mixed disulfide) consistently decreased with increasing doses of D-penicillamine. In two normal subjects treated with D-penicillamine, total cystine excretion increased dramatically and appeared to be dose related.

The dissolution of cystine calculi, secondary to massive fluid intake and penicillamine administration, is both fascinating and extremely important in planning a therapeutic regime in a particular case. As previously described Dent (3) has achieved complete dissolution of cystine stones over a long period of time by massive fluid intake. The hyposaturated solution of cystine in the urine as compared to that in the stone permits slow but continued dissolution of the stone if no other deposits (uric acid, calcium, phosphates) form part of the stone. Numerous reports (9, 10, 11, 14, 16) as well as our case (HG) document the rapid dissolution of cystine stones under penicillamine administration. The high concentration of penicillamine in the urine bathing the calculus combines with the cystine molecule on the exterior of the calculus, forming the mixed disulfide, thereby slowly decreasing the size of the stone. The presence of constituents other than cystine in the stone (as with the method of massive fluid intake) would prevent the dissolution. It would seem prudent to try a combination of both massive fluid intake and

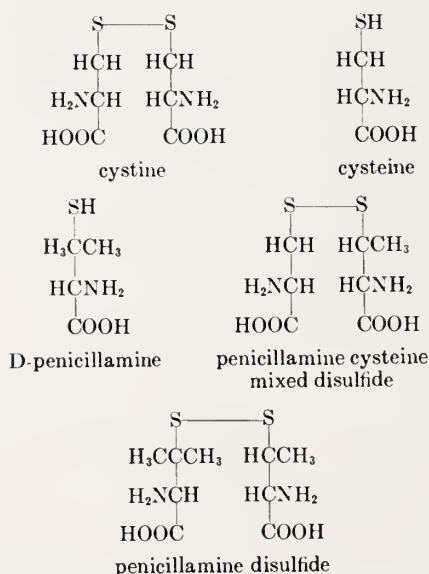


Fig. 7. Chemical formula of cystine, D-penicillamine and related disulfides.

D-penicillamine therapy in newly presented cases of cystinuria before elective surgery is carried out.

There appears to be more than a coincidental relationship between hyperuricemia and cystinuria. In Boyce's series (11) 11 of 22 cystinuric patients had elevated blood uric acids. Meloni (17) reports four cases in which many of the patients' relatives had asymptomatic hyperuricemia. King's (18) and our case are additional examples of this entity.

Toxicity

The toxicity of D-penicillamine should be distinguished from that of L-penicillamine which is quite toxic. The latter should not be used nor should the mixed iso DL-penicillamine. In a significant number of patients an urticarial rash, high fever, joint pain, and adenopathy develops between the 7th and 10th day after starting D-penicillamine. In Crawhall's original seven patients, two such reactions occurred (19). A review of the papers published since then reveals that about 30% will experience this initial allergic reaction (8, 9, 20).

Most investigators have temporarily discontinued the medication and treated the reaction with antihistamines and at times steroids. Treatment is then restarted at a very small initial dosage which is increased by slow increments (coincident with antihistamine therapy) until the full dosage is reached. Most reactions treated in this manner have been successfully overcome. Other investigators have not discontinued the medication but just have reduced the dosage temporarily and have overcome the allergic reaction with antihistamines (as in our two cases).

Inasmuch as D-penicillamine is a natural degradation product of penicillin it could be assumed that cross reactivity would occur. This has been shown in some cases but successful use of this medication has been achieved in patients allergic to penicillin (9). The case of desensitization of patients to D-penicillamine, in complete contrast to the reported experience with patients intolerant to penicillin, weighs against any close similarity between the mechanisms of sensitivity of the two drugs. However, it should be remembered that penicillin is antagonistic to penicillamine and the two drugs cannot be used simultaneously.

D-penicillamine potentially may produce iron depletion and this has been shown to have occurred in a number of cases (3, 16, 21). It has been reported as well in patients with Wilson's disease under treatment. Prophylactic oral use of iron in large amounts should be avoided as it may bind the penicillamine in the gastrointestinal tract, nullifying the effectiveness of the penicillamine. Iron may be given parenterally or intermittently by mouth a few days a week.

It has been reported that D-penicillamine may have a mild antipyridoxine effect and most investigators have given their patients 50 mg of pyridoxine daily, prophylactically (3, 22). Other investigators have failed to substantiate

this acquired deficiency, K. Gibbs (23) having found no evidence of it in 19 patients. This is in marked contrast to L-penicillamine which has a definite and marked antipyridoxine effect (9).

There have been no reported complications with patients taking this drug during pregnancy and several successful pregnancies have been carried out (9, 20).

Prolonged administration of D-penicillamine for over a year to patients with Wilson's disease has been associated with extravasations of blood into the skin, particularly at sites subject to pressure or trauma over bony prominences, such as the skin over the knees, shoulders, elbows, and buttocks (8). These lesions are not progressive and usually heal, leaving pigmented areas or excessive wrinkling of the skin. Protection of the pressure points and temporary reduction in dosage resulted in decreased severity of this lesion.

A subjective loss of taste for salt and sweet developed in a third of the patients in one series (7 of 20 patients) on penicillamine (24). Further testing revealed decreases in taste acuity for sour and bitter as well. Upon discontinuation of the medication subjective taste returned to normal within four to six weeks in all patients.

A marked leukopenia developed in five of Sternlieb's and Scheinberg's patients (given for Wilson's disease) promptly after starting therapy, and in two, this abnormality was the only manifestation of toxicity (8). Thrombocytopenia occurred in 3 patients, all of whom suffered from other side effects of the drug. Both leukopenia and thrombocytopenia subsided within days after discontinuing therapy. Anemia was not observed as a toxic effect in their series.

Two cases of neutrophilic agranulocytosis were reported in rheumatoid arthritic patients within five weeks after being placed on D-penicillamine (20). One died from sepsis while the other recovered. Previous adrenocorticosteroid therapy may have played a role in the development of the hematological toxicity in these patients.

A case of optic neuritis occurring in a patient with Wilson's disease on DL-penicillamine is reported in which prompt remission was achieved coincident with pyridoxine therapy (25). Another case is reported, however, in which a patient with Wilson's disease, on DL-penicillamine experienced optic neuritis while on prophylactic pyridoxine. The neuritis in this case resolved without stopping penicillamine (26).

Nephrotic Syndrome

The most serious complication of penicillamine therapy has been the development of the nephrotic syndrome. The first eight reported cases were reviewed in 1966 (27) and it was concluded that it only occurred with the DL isomer of penicillamine. Our case (DB) and other recent cases have clearly shown that it also occurs with the D isomer. Of the eight original cases reviewed, one died in acute renal failure, one died from hematemesis (prednisone

administration following improvement of the nephrotic syndrome), one had a remission but the nephrotic syndrome recurred when the DL isomer was restarted; two had remissions which continued during D-penicillamine administration and two had remissions that were not further challenged with any form of penicillamine. As much as 45 gm of protein daily has been excreted in one patient at the height of the reaction (28).

In Adam's case (29) a renal biopsy revealed focal glomerulitis with hyalinization of the lobules and obliteration of the loop.

A ninth case is reported (30) of a nine-year-old girl in whom the nephrotic syndrome developed with fatal outcome after administration of the DL isomer.

At least two other cases have occurred in patients with Wilson's disease. In one of these the renal biopsy revealed membranous glomerulonephritis (31).

Rosenberg et al (32) reported on three cystinurics who suffered marked proteinuria on D-penicillamine therapy. The proteinuria disappeared after stopping treatment. In 2 patients, the proteinuria developed after they had been on therapy 2 and 4 months and in the third case, after 3 years of drug therapy. This last patient had experienced no prior manifestations of any drug toxicity while the former two had experienced fever and generalized skin rash. Renal biopsies on all three patients revealed a distinct focal glomerulonephritis.

Felts reports a case in which severe proteinuria (3.5 gm protein/day) had persisted for 12 months after stopping penicillamine.

Luke (33) reports two cases in whom proteinuria developed while on penicillamine therapy. The proteinuria continued in the first case for 30 months—despite stopping the drug, while in the second case the proteinuria persisted for two months and then ceased spontaneously, while continuing medication throughout that period of time. This latter case has great significance (as in our case DB) for patients who have severe uncontrollable cystinuria and who experience marked proteinuria on therapy.

Summary

1) Our experience with D-penicillamine in cystinuric patients over the past five years verifies previous reports of its effectiveness. It has altered favorably a poor prognosis in many youthful patients who were destined for innumerable surgical and cystoscopic procedures as well as futile medical management.

2) Four cases are presented in detail to portray the great difficulty in management prior to the introduction of penicillamine with the satisfying results achieved despite difficulties encountered with the use of the medication.

3) Both the early and late complications of the drug have been reviewed in detail. These are often serious and at times fatal. The acute toxic reaction occurring in a third of the patients can be controlled with antihistamines, temporary reduction in dosage and, if necessary, steroids and need not be feared. The nephrotic syndrome, a complication in one of our patients, is reviewed and merits frequent periodic urine checks for albumin in all patients

taking the drug. It may be possible to overcome the nephrotic reaction despite continuation of D-penicillamine (case DB) but this cannot be stated with certainty at this time.

4) In view of the frequent serious and occasional fatal reaction to the drug it would seem prudent to attempt therapy without penicillamine in fresh cases of cystinuria where cystine excretion studies and the clinical picture permit. A significant number of cases can be handled in this fashion.

5) An attempt at stone dissolution by combining D-penicillamine and high fluid intake should be tried before elective surgical removal of calculi is undertaken. In a significant percentage of cases the calculi (if pure cystine) can be completely, or partially, dissolved.

6) If the patient cannot tolerate the usual full dosage of medication, as in some of our cases, the largest possible dose should be given just prior to retiring at night, as this is the period of greatest saturation of the urine by cystine and the time at which a nidus for stone formation most likely occurs. The period of wakefulness can then be handled more readily by increased fluid intake and alkalinization of the urine.

Acknowledgment

Dr. Elmer Alpert of Merck, Sharpe & Dohme supplied the D-penicillamine (Cuprimine).

References

1. Crawhall, J. C., Scowen, E. F., and Watts, R. W. E.: Effect of Penicillamine on Cystinuria, *Brit Med J* 1:588-590, 1963.
2. Dent, C. E., and Senior, B.: Studies on the Treatment of Cystinuria, *Brit J Urol* 27: 317-332, 1955.
3. Bartter, F. C. et al: Cystinuria—Clinical Staff Conference, *Ann Int Med* 62 No. 4:796-822, 1965.
4. Smith, D. R., Kolb, F. O., and Harper, H. A.: The Management of Cystinuria and Cystine Stone Disease, *J Urol* 81:61-69, 1959.
5. Collini, W. R. et al: Methods of Diminishing Cystine Excretion in Cystinuria, *J Urol* 93:729-734, 1965.
6. Zinneman, H. H., and Jones, J. E.: Dietary Methionine and Its Influence on Cystine Excretion in Cystinuria Patients, *Metabolism* 15:915-921, 1966.
7. Dent, C. E., Friedman, M., Green, H., and Watson, L. C. A.: Treatment of Cystinuria, *Brit Med J* 1:403-408, 1965.
8. Sternlieb, I., and Scheinberg, I. H.: Penicillamine Therapy for Hepatolenticular Degeneration, *JAMA* 189:748-754, 1964.
9. Lotz, M., et al: D-penicillamine Therapy in Cystinuria, *J Urol* 95:257-263, 1966.
10. Lotz, M., and Bartter, F. C.: Stone Dissolution with D-penicillamine in Cystinuria, *Brit Med J* 2:1408-9, 1965.
11. Boyce, W. H., Smith, M. J. V., and King, Jr., J. S.: Some Observations on the Use of D-penicillamine in the Treatment of Cystinuria, *Urol Digest* 19-23, 1968.
12. Crawhall, J. C., Scowen, E. F., and Watts, R. W. E.: Further Observations on Use of D-penicillamine in Cystinuria, *Brit Med J* 1:1411-1413, 1964.
13. King, Jr., J. S., and Boyce, W. H.: Effect of Penicillamine on Cystinuria, *Invest Urology* 2:595-597, 1965.
14. Lotz, M., and Bartter, F. C.: Treatment of Cystinuria, *Brit Med J* 1:855, 1965.

15. MacDonald, W. B., and Fellers, F. X.: Penicillamine in the Treatment of Patients with Cystinuria, *JAMA* 197(6):396-402, 1966.
16. McDonald, J. E., and Henneman, P. H.: Stone Dissolution in Vivo and Control of Cystinuria with D-penicillamine, *NEJ Med* 273(11):578-593, 1965.
17. Meloni, C. R., and Canary, J.: Cystinuria with Hyperuricemia, *JAMA* 200(3):257-9, 1967.
18. King, Jr., J. S., and Wainer, A.: Cystinuria with Hyperuricemia and Methioninuria, *Am J Med* 43:125-130, 1967.
19. Crawhall, J. C.: Personal Communication, July 10, 1963.
20. Corcos, J. M., et al: Neutrophilic Agranulocytosis during Administration of Penicillamine, *JAMA* 189:265-268, 1964.
21. Scheinberg, I. H., and Sternlieb, I.: Environmental Treatment of Wilson's Disease, *Ann Int Med* 53:1151-1161, 1960.
22. Jaffe, I. A., Altman, K., and Merryman, P.: The Anti-pyridoxine Effect of Penicillamine in Man, *J Clin Invest* 43:1869, 1964.
23. Gibbs, K.: Penicillamine and Pyridoxine Requirement in Man, *Lancet* 1:175, 1966.
24. Keiser, H. R., Henkin, R. I., Bartter, F. C., and Sjoerdsma, A.: Loss of Taste during Therapy with Penicillamine, *JAMA* 203: 381-383, 1968.
25. Tu, J., Blackwell, R. Q., and Lee, P. F.: DL-penicillamine as a Cause of Optic Axial Neuritis, *JAMA* 185: 83-86, 1963.
26. Goldstein, N. P., Hellenhorst, R. W., Randell, R. V., and Gross, J. B.: Possible Relationship of Optic Neuritis, Wilson's Disease, and DL-penicillamine, *JAMA* 196:734-5, 1966.
27. Sternlieb, I.: Penicillamine and the Nephrotic Syndrome, *JAMA* 198:13112, 1966.
28. Hirschman, S. Z., and Isselbacher, K. J.: The Nephrotic Syndrome as a Complication of Penicillamine Therapy for Hepatolenticular Degeneration (Wilson's Disease), *Ann Int Med* 62(6):1297-1300, 1965.
29. Adams, D. A., Goldman, R., Maxwell, M. H., and Latta, H.: Nephrotic Syndrome Associated with Penicillamine Therapy of Wilson's Disease, *Am J Med* 36:330-336, 1964.
30. Karp, M., Lurie, M., and Yonis, Z.: Nephrotic Syndrome in the Course of Treatment of Wilson's Disease with DL-penicillamine, *Arch Dis Children* 41:684, 1966.
31. Scheinberg, I. H.: Personal Communication, Feb. 1968.
32. Rosenberg, L. E., and Hayslett, J. P.: Nephrotoxic Effects of Penicillamine in Cystinuria, *JAMA* 201:698-9, 1967.
33. Luke, R.: Letters To The Editor, *JAMA* 203:367-8, 1968.

Received for publication September 2, 1968

The Occurrence of Type B-Wolff-Parkinson-White Conduction in the Presence of Right Bundle Branch Block

STEPHEN RICHMOND, M.D.* AND LEON PORDY, M.D.

In 1930 Wolff, Parkinson and White (1) described the electrocardiographic findings of a short P-R interval with a wide QRS complex occurring in patients prone to paroxysmal tachycardias. Since then this syndrome has been widely recognized, and the electrocardiographic findings have been estimated to occur in 0.16% of asymptomatic subjects (2). The incidence of bundle branch block and Wolff-Parkinson-White syndrome (WPW) occurring together has been estimated to be 0.0024% (3). Pick and Fisch (3) and Castellanos et al (4) have reported right bundle branch block (RBBB) and left bundle branch block (LBBB) in the presence of type A-WPW.

As a result of experimental induction of RBBB in man, Gamboa et al (5) concluded that in type A-WPW, the anomalous ventricular conduction originates in the left ventricle and spreads posteroanteriorly, whereas in type B-WPW, the anomalous ventricular conduction must originate in the right ventricle and spreads anteroposteriorly. Gamboa et al presented the electrocardiogram and vectorecardiogram of a patient with type B-WPW alternating with normal ventricular conduction, whose QRS complexes of WPW were unchanged by the experimental induction of RBBB. Recently, the electrocardiogram of a case of RBBB alternating with type B-WPW was reported (6).

The transitory occurrence of type B-WPW in a patient with RBBB has enabled us to study this combination by means of the vectorecardiogram with computer analysis as well as by the standard 12-lead electrocardiogram.

Case Report

J.R., a 39-year-old man, suddenly noted the onset of recurrent paroxysms of palpitation, a few minutes in duration and associated with diaphoresis but not chest pain. One week later he was examined in the emergency room of The Mount Sinai Hospital in New York because of an episode of palpitation of five hours' duration. An electrocardiogram showed supraventricular tachycardia, rate 145 per minute, and the patient was treated with meperidine, secobarbital, and deslanoside and was discharged on digoxin 0.25 mg per day. The patient experienced no further episode of tachycardia. Two weeks later when seen in the outpatient clinic he was found to be hypertensive and the electrocardiogram disclosed Wolff-Parkinson-White conduction. He was admitted to the hospital and digoxin was discontinued at that time.

On admission he was found to be a well-developed man in no distress. Blood pressure was 180/110 mm Hg; respirations-20/min; pulse-80/min and regular; and the temperature was 98.6 F. Ocular fundi exhibited grade II hypertensive retinopathy. Examination of the heart revealed the PMI to be in the 5th left intercostal space; A2 was greater than P2 and there was a grade I/VI apical systolic murmur. A fourth heart sound was noted on

From the Cardiographic Laboratory, The Mount Sinai Hospital, New York.

* This work was done during the tenure of USPHS Research Fellowship in Cardiology I-F2-HE-32,27701 at The Mount Sinai Hospital, N.Y., N.Y.

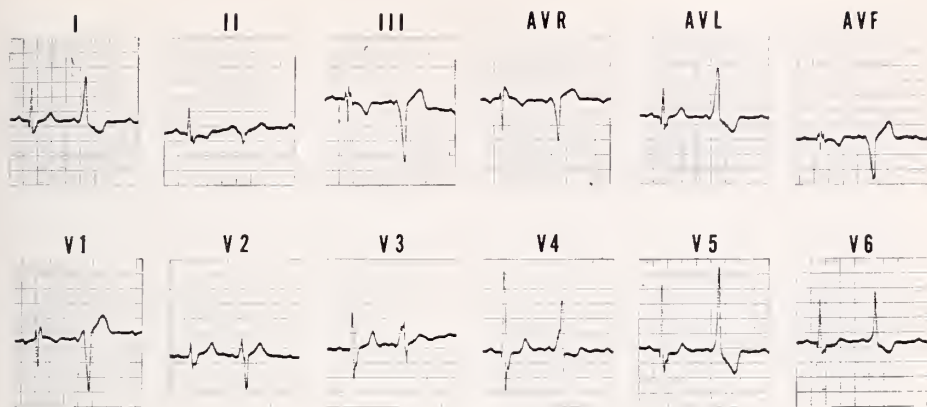


FIG. 1. J.R., ♂, 48 yrs. Electrocardiogram discloses right bundle branch block alternating with Wolff-Parkinson-White syndrome-type B. The first complex of each lead shows right bundle branch block and the second complex of each lead shows Wolff-Parkinson-White-type B.

the phonocardiogram. The hemogram was normal and the urinalysis showed a specific gravity of 1.002, trace of albumin, 3-4 RBC and 1-4 WBC per high power field. The chest x-ray showed the heart to be markedly enlarged in the transverse diameter. The intravenous pyelogram and urinary catecholamines were normal. The initial electrocardiogram showed regular sinus rhythm and right bundle branch block alternating with Wolff-Parkinson-White conduction. (Fig. 1) His QRS pattern was always complete right bundle branch block except at times when he spontaneously exhibited complexes of Wolff-Parkinson-White conduction. This suggests that the right bundle branch block was persistent even during the presence of WPW conduction. Neither right nor left carotid sinus pressure elicited WPW conduction.

Method

The X, Y, and Z orthogonal leads of the vector-cardiogram (Frank system) were recorded simultaneously on a Sanborn-Ampex model 2000 tape recorder by means of three Sanborn 350-2700 high gain preamplifiers. This analogue tape was then played through a Sanborn model 322 dual channel D.C. amplifier recorder. Two orthogonal leads were printed simultaneously in strip chart form (Fig. 2). By means of a timing device, the tape was then played into a Sanborn model 670A, X-Y recorder and the vectorecardiogram was recorded on Kodak Linagraph Print Paper. By monitoring the strip chart of the orthogonal leads, it was possible to photograph selectively those vector loops showing RBBB and then those disclosing wpw (Fig. 3). The vectorecardiogram during RBBB showed normal P loops and intact septal depolarization. In the frontal plane, the QRS loop was noted to have a figure-of-eight configuration. The terminal portion of the QRS loop exhibited slowing, and was directed to the right and superiorly. There was an S-T vector directed superiorly, anteriorly, and slightly to the right; the T loops were discordant. When wpw conduction occurred, the P loops were essentially unchanged, but in the frontal plane the QRS loops were inscribed in a clockwise direction and were directed to the left, superiorly, and posteriorly. The efferent portion of the

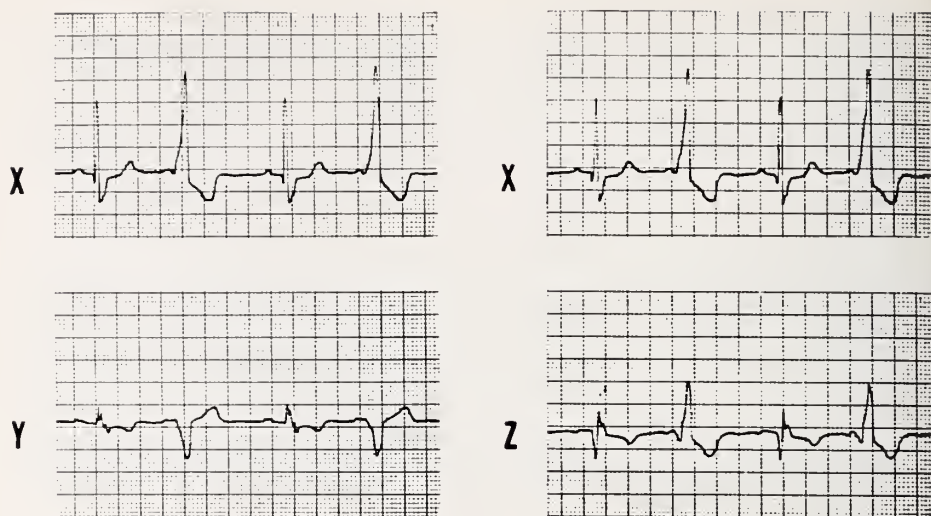


FIG. 2. J.R., ♂, 48 yrs. Simultaneous orthogonal leads (Frank system): right bundle branch block in the first and third complexes and Wolff-Parkinson-White conduction-type B in the second and fourth complexes.

loops (delta wave) showed marked slowing and was directed to the left superiorly and posteriorly. An S-T vector was directed anteriorly, to the right and slightly superiorly; and the T loops were discordant.

The original tape was processed through an experimental IBM 9×12 Analogue-to-Digital Converter (7) utilizing an IBM "1401" computer system (8). The orthogonal leads were digitized at a rate of 400 per second and a plot of the orthogonal values at these time intervals was obtained. In addition, a computer print-out was produced containing the magnitude and angles of the spatial vectors as well as the vector values in the frontal, horizontal, and left sagittal planes at each interval. By means of this print-out accurate measurements of the P wave duration, P-R interval, P-J interval, QRS duration and delta wave duration were obtained in units of $1/400$ second, Table I.

Discussion

The electrocardiogram in this case (Fig. 1) showed regular sinus rhythm with right bundle branch block alternating with a different QRS complex which disclosed Wolff-Parkinson-White conduction. The latter revealed typical delta waves, prolonged QRS duration and dominant S waves in the right precordium corresponding to type B-WPW conduction (9). During this type B-WPW conduction, the terminal slowing characteristic of RBBB is absent (Fig. 2). In sharp contrast, the terminal slowing of RBBB has been observed in type A-WPW (4), indicating a difference in the pathway of conduction between type A and type B-WPW.

The planar Frank vectorcardiogram (Fig. 3) in the case of the RBBB com-

R.B.B.B.*

W.P.W.**

FRONTAL



LEFT SAGITTAL



HORIZONTAL

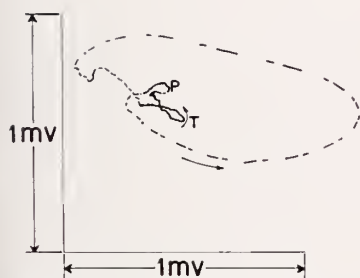


FIG. 3. J.R., ♂, 48 yrs. Frank vectorcardiograms: Planar projections with: * Right Bundle Branch Block and ** Wolff-Parkinson-White conduction. Timing interruptions every $\frac{1}{333}$ second; sense of direction is from dash to dot.

plexes shows normal septal depolarization with the terminal portion of the QRS delayed and directed to the right. However, with wpw conduction the QRS loop is completely different; the initial vector shows marked slowing (delta wave) and is directed at first anteriorly, superiorly and to the left. This initial vector satisfies the criteria for type B-wpw in the Cube system (the delta wave being oriented to the left and between -60° and $+30^\circ$ in the horizontal plane) (10). It has been shown (11, 12) that the mean angular values for the initial portion of the QRS vector loop in the Cube and Frank systems are equivalent. Therefore, although we have utilized the Frank system, we have applied the above angular data for labeling the vectorcardiogram in this case type B-wpw.

TABLE I
Computer Processed Frank Vectorcardiogram: Wave Durations

	P wave	P-R interval	QRS complex*	P-J interval**	Delta wave
RBBB	41	66	55	121	0
WPW Type B	42	44	57	101	32

The vectorcardiographic measurements in RBBB and Type B-WPW are in units of 1/400 second. Note that the shortening of the P-J interval with WPW conduction is accounted for by the shortened P-R interval since the QRS durations are similar. The delta wave accounts for more than half of the QRS duration in WPW conduction.

* QRS complex refers to the time from onset of the delta wave to completion of the S wave.

** P-J interval refers to the time from P onset through QRS termination.

The delta wave in this case is similar to that reported by Burchell et al (13) in a case of type B-WPW who also ascribed it to initial activation of the free wall of the right ventricle. The terminal portion of the QRS loop with WPW conduction also differs markedly from the loop during RBBB, now being directed to the left, posteriorly and superiorly. Thus, the QRS loops in the presence of type B-WPW are completely different from those during RBBB and show no evidence of RBBB in their terminal portions.

In this case, the occurrence of type B-WPW in the presence of RBBB decreased the P-J interval appreciably, accounted for by a shortening of the P-R interval (Table I). The delta wave was noted to account for more than half of the QRS duration and ended at a time interval corresponding to 10/400 second after the start of the QRS of the RBBB beats. However, while there was slight lengthening of the QRS duration to 57/400 second, the terminal portion of the QRS complex with type B-WPW was completed a full 20/400 of a second before the QRS of the RBBB ended. Thus, during type B-WPW with RBBB, there is no terminal delay of QRS conduction in the WPW complexes indicating that the right ventricular muscle is depolarized early in the cardiac cycle in contrast to the late depolarization which occurs in uncomplicated RBBB. These observations suggest that in type B-WPW atrioventricular conduction occurs by an anomalous pathway to the anterior portion of the right ventricle. The wave of depolarization then spreads over the right ventricle and may enter the right bundle branch system distal to the site of block.

It must be considered that in type B-WPW conduction, ventricular depolarization starts anteriorly and proceeds in a posterior direction, whereas with type A-WPW conduction, ventricular depolarization starts posteriorly and then spreads anteriorly. These findings are in agreement with those of Gamboa et al (5) and Shamroth and Krikler (6) who concluded that type B-Wolff-Parkinson-White conduction is anomalous and bypasses the area of the conduction system involved during right bundle branch block. This indicates that type B-Wolff-Parkinson-White conduction is not due to accelerated conduction in a normal pathway, since if this were true, type B-WPW in the presence of RBBB should show terminal QRS delay as does type A-WPW with RBBB.

Although during type B-WPW conduction plus RBBB, the initial portion of the P wave is the same as with RBBB alone and the P-P intervals are constant, there are minor differences in the configuration of the latter half of the P wave. Actually, measurements made of the onset of the QRS are subject to error since the beginning of ventricular depolarization in wpw (delta wave) may be occurring simultaneously with the inscription of the latter part of the P wave. The P wave differences between beats with normal A-V conduction and those with wpw conduction may be accounted for by a fusion of the P wave and delta waves.

Summary

A case of intermittent type B-Wolff-Parkinson-White conduction in the presence of right bundle branch block is presented and studied by means of the electrocardiogram, vectorcardiogram and computer analysis. The enhancement of measurement accuracy afforded by the digital computer with a high sampling rate was utilized in this study. During the occurrence of type B-wpw, there was no evidence of the terminal delay characteristic of right bundle branch block. Accelerated conduction through normal pathways is considered incompatible with this finding. Therefore, the data obtained in this case support the hypothesis that type B-wpw involves depolarization of the ventricles by conduction from the right atrium to the right ventricle via an anomalous pathway.

References

1. Wolff, L., Parkinson, J., and White, P. D.: Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *Am Heart J* 5:685, 1930.
2. Averill, K. H., Fosmol, R. J., and Lamb, L. E.: Electrocardiographic Findings in 67,375 Asymptomatic Subjects. IV. Wolff-Parkinson-White Syndrome, *Am J Cardiol* 6:108, 1960.
3. Pick, A., and Fisch, C.: Ventricular Pre-excitation (WPW) in the Presence of Bundle Branch Block, *Am Heart J* 55:504, 1958.
4. Castellanos, A., Jr., Mayer, J., and Lemberg, L.: The Electrocardiogram and Vectorcardiogram in Wolff-Parkinson-White Syndrome Associated with Bundle Branch Block, *Am J Cardiol* 10:657, 1962.
5. Gamboa, R., Peñaloza, D., Sime, F., and Banchero, N.: The Role of the Right and Left Ventricles in the Ventricular Pre-excitation (WPW) Syndrome. An Experimental Study in Man, *Am J Cardiol* 10:650, 1962.
6. Schamroth, L., and Krikler, D. M.: Location of the Pre-excitation Areas in the Wolff-Parkinson-White Syndrome, *Am J Cardiol* 19:889, 1967.
7. Alexander, D. C., and Wortzman, D.: Computer Diagnosis of Electrocardiograms I. Equipment, Computers and Biomedical Research, 1:348, Feb. 1968.
8. Pordy, L. et al: Method for Digital Computer Presentation of the Spatial Vectorcardiogram, 1969 (To be published.)
9. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnson, F. D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), *Am Heart J* 29:281, 1945.
10. Bleifer, S., Kahn, M., Grishman, A., and Donoso, E.: Wolff-Parkinson-White Syndrome. A Vectorcardiographic, Electrocardiographic and Clinical Study, *Am J Cardiol* 4:321, 1959.

11. Gunther, L., and Graf, W. S.: The Normal Adult Spatial Vectorcardiogram. The Timed Sequence of Inscription of the QRSs of the Cube and Frank Systems, *Am J Cardiol* 15:656, 1965.
12. Pordy, L. et al: Digital Computer Presentation of the Spatial Vectorcardiogram: Cube versus Frank Methods. 1968 (To be published).
13. Burchell, H. B., Frye, R. L., Anderson, M. W., and McGoon, D. C.: Atrioventricular and Ventriculoatrial Excitation in Wolff-Parkinson-White Syndrome (Type B): Temporary Ablation at Surgery, *Circulation* 36:663, 1967.

Received for publication September 9, 1968

Experimental Teratogenesis in Ferrets Using Rubella Virus†

TERESITA S. ELIZAN, M.D.,* AKINYELE FABIYI,* PH.D. AND
JOHN L. SEVER, M.D., PH.D.

The purpose of the present study is to report the results and some of the problems encountered in a series of experiments to evaluate the possible teratogenic effect of rubella virus in the ferret model. Previous work by Fabiyi et al (1) demonstrated chronic rubella infection of newborn ferrets after inoculation with rubella virus by various routes. Specific complement-fixing and neutralizing antibodies persisted in these animals for at least a year after inoculation. Preliminary work by these authors (2, 3) has shown transplacental infection in pregnant ferrets inoculated with rubella virus by the subcutaneous route 48 to 72 hours post-mating. Virus was isolated from 80 per cent of the inoculated animals killed between days 10 through 29 postinfection. Only 25 per cent of the virus-positive infected ferrets had infected fetuses.

Material and Methods

Virus. The RB strain of rubella virus grown in the primary African green monkey kidney (AGMK) tissue culture was used. The history of the virus and number of passages in AGMK tissue culture (14th passage) had previously been described (1). The virus had a tissue culture infective dose ($TCID_{50}$) of $10^{4.5}$ per ml. The virus, and a corresponding virus-negative tissue culture fluid which had the same number of tissue culture passages as the virus, were tested and confirmed to be free of detectable contaminating viruses, bacteria, fungi, and mycoplasma. The methods of virus isolation and identification have been described (1).

Animal inoculation. Normal adult female ferrets (*Mustela putorius furo*) which had been vaccinated against distemper virus and determined to be free of detectable antibodies to rubella virus were used. They were supplied by a commercial source (Gilman Marshall, North Rose, New York) and received in the laboratory within 24 to 48 hours after mating. All animals were fed a diet which consisted of fresh horse meat, fresh beef liver, dried Brewer's yeast, pulverized chick egg shells or limestone, cod liver oil, and homogenized pasteurized milk. Two schedules of inoculations were employed. One set of animals was inoculated subcutaneously with a single dose of one ml of rubella virus containing 32,000 $TCID_{50}$ within 24 hours after arrival in the

From the Section on Infectious Diseases, Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

* Present address: Department of Neurology, Laboratory of Neurovirology, The Mount Sinai School of Medicine, New York, New York 10029.

† Presented at the Eighth Annual Meeting of the Teratology Society, at Buck Hill Falls, Pa., on May 15-17, 1968.

laboratory (day 2 to 3 of gestation). Corresponding control animals received one ml of rubella-negative tissue culture fluid. The second set of animals was inoculated subcutaneously on the first, third, and fifth day of arrival (approximately day 2, 4, 6 of gestation) with 0.5 ml of rubella virus containing 15,900 TCID₅₀ per dose per day. Corresponding control animals received 0.5 ml of rubella-negative tissue culture fluid at the same time intervals as the test animals. A third control group consisted of pregnant animals that were not inoculated. Throat swabs from all mothers were taken on days 12, 13, 14, 15, 16, and 17 after initial inoculation. The rubella-inoculated group (Group I) consisted of 12 mothers which had single inoculations and 15 mothers with multiple inoculations. The tissue culture fluid control group (Group II) consisted of 8 mothers with single and 15 mothers with multiple inoculations. The uninoculated control group (Group III) consisted of 19 mothers.

At 36 to 39 days of gestation (3-6 days before delivery), the animals were killed and the uterus and its contents removed by laparotomy. The number of resorptions, viable and dead fetuses, and the condition of the placentas were recorded; in addition, the fetal birth weight and length and any gross abnormality were immediately noted before fixation of the fetuses in Bouin's and/or formalin. A more detailed gross examination of all organs after fixation was done by serial razor blade cross sections of the head and abdomen, and cardiovascular examination was done using a dissecting microscope. Microscope sections were made of all fetuses with gross abnormalities and of selected grossly normal ones in the same group.

Results

Table I shows the pregnancy outcome of the mothers in the three groups.

Group I (Rubella-inoculated). The 12 ferret mothers which received a single dose of rubella virus between day 2 to 3 of gestation had a total of 104 pregnancies, 75 of which were viable, normal fetuses. Three of these mothers had all resorptions and accounted for 20 of the 25 resorption sites found in the

TABLE I
Pregnancy Outcome of Mothers in Rubella-Inoculated and Control Groups

	Grp. I (Rubella Inoculated)				Grp. II (Tissue Culture Fluid-Inoculated Control)				Grp. III (Uninoculated control)	
	Single Inoc.		Multiple Inoc.		Single Inoc.		Multiple Inoc.		Resorbed	Abnormal
	Re- sorbed	Ab- normal	Re- sorbed	Ab- normal	Re- sorbed	Ab- normal	Re- sorbed	Ab- normal		
Pregnancy outcome	25/104 (24%)	4/104 (3.8%)	16/134 (11.9%)	8/134 (6.0%)	5/68 (7.4%)	10/68 (14.7%)	19/140 (13.6%)	1/140 (0.7%)	11/182 (6.0%)	1/182 (0.5%)
Ratio of mothers with resorbed and abnormal fetuses	6/12 (50%)	2/12 (16.6%)	10/15 (66.6%)	2/15 (13.3%)	4/8 (50%)	4/8 (50%)	8/15 (53.3%)	1/15 (6.6%)	6/19 (31.6%)	1/19 (5.3%)

entire group. One mother had no resorptions, but had one fetus with a vestigial tail. Another mother had 3 resorptions and 3 fetuses with exencephaly. Congenital malformation rate was 3.8% while the resorption rate was 24% in this group.

The 15 ferrets which had serial, multiple doses of rubella virus from days 2 through 6 of gestation had a total of 134 pregnancies, 110 of which were normal fetuses. Ten mothers accounted for 16 resorption sites. Two mothers had no resorptions, but each had 3 and 5 abnormal fetuses, respectively. The overall resorption and abnormality rates in this group were 11.9% and 6.0%, respectively. Abnormalities included vestigial tail, cleft lip and palate, kyphoscoliosis, microcephaly, exencephaly, and cervical spina bifida.

Group II (Tissue Culture Fluid-Inoculated). Eight ferrets inoculated once with TCF between day 2 to 3 of gestation had a total of 68 pregnancies, 53 of which were normal fetuses. Four had 5 resorption sites; 2 of these also had 4 abnormal fetuses. Two others had no resorptions but had 6 abnormal fetuses. Resorption and congenital malformation rates were 7.4% and 14.7% respectively. Abnormalities included cleft lip and palate, kyphoscoliosis, exencephaly, cervical spina bifida, omphalocele, and syndactyly.

Fifteen ferrets inoculated serially with TCF from days 2 through 6 of gestation had a total of 140 pregnancies, of which 120 were normal fetuses. Eight accounted for 19 resorptions; one of these also had an abnormal fetus with exencephaly, cervical spina bifida, microcephaly, and an absent right upper limb. The resorption and malformation rates in this group were 13.6% and 0.7%, respectively.

Group III (Uninoculated Control). Nineteen ferrets which were not inoculated had a total of 182 pregnancies, of which 170 were viable, normal fetuses. Six had 11 resorptions, and one mother had an abnormal fetus with a cleft palate. These were equivalent to spontaneous resorption and congenital abnormality rates of 6.0% and 0.5%, respectively.

No further gross or microscopic abnormalities were demonstrated in the rest of the tissues and organs of all the animal groups examined.

The distribution of the animals with abnormal fetuses within the 3 groups in the 7 experiments (Table II) showed that 10 mothers accounted for all of the 24 abnormal fetuses. Four mothers were in the rubella-inoculated group, 5 were in the TCF-inoculated control group, and one was in the uninoculated control group. The distribution of these mothers in the 3 groups appears to be at random, except in the first experiment (A) where 60% of the mothers in the rubella group, 50% of the mothers in the TCF group, and none of the mothers in the uninoculated group had abnormal fetuses.

Discussion

The spontaneous resorption and malformation rates in the uninoculated control group are almost the same as the resorption rate in the TCF-single inoculation group and the congenital malformation rate in the TCF-multiple inoculation group. The almost twice as high resorption rate in both the TCF

TABLE II
*Distribution of Mothers with Abnormal Fetuses within the Test and Control Groups
 in Seven Experimental Trials*

Experiment (date)	No. of Mothers with Abnormal Fetuses/ Total No. of Mothers in each Group			Total
	Grp. I	Grp. II	Grp. III	
* A (8/9/66)	3/5	2/4	0/4	5/13
B (9/9/66)	0/3	0/2	0/1	0/6
C (9/15/66)	0/5	0/3	0/3	0/11
* D (1/1/67)	1/4	0/2	0/0	1/6
* E (4/14/67)	0/2	1/1	0/1	1/4
F (6/12/67)	0/6	0/3	0/2	0/11
* G (1/11/68)	0/2	2/8	1/8	3/18
Total	4/27	5/23	1/19	10/69
Total No. of Fetuses with Abnormalities/ Total No. of Pregnancies				
	12/238	11/208	1/182	24/628

* Positive Experiments.

and rubella virus multiple inoculation groups, compared to that of the uninoculated control and singly-inoculated TCF group, may possibly only reflect the role of increased handling and trauma to the former groups inherent in the serial inoculations, rather than a true biological difference between the groups. The significant 24 per cent resorption rate in the singly-inoculated rubella virus group which is twice as high as that of the multiply-inoculated rubella and TCF groups is mainly accounted for by three mothers with all resorptions; whether these resorptions are due to the virus, however, cannot be determined. There is no significant difference in the malformation rate of the singly-inoculated and multiply-inoculated rubella virus group.

Singly-inoculated TCF group had the highest congenital malformation rate. If one were to postulate an undetected teratogenic contaminating agent in the tissue culture fluid (which should be present in both the RV and TCF groups), one would still expect the rates to be higher in the rubella group than in the TCF group, if rubella virus itself were truly playing an additional teratogenic role. But the results are just the opposite, unless one further speculates that the contaminating agent has a mutually inhibitory effect on rubella virus.

Placental transfer of the virus can be expected to occur in 20 per cent of the originally RV-inoculated mothers (2, 3). However, we have no data on what percentage of infected fetuses would develop congenital abnormalities. Even presuming that all infected fetuses would develop malformations, the chances of having an inoculated mother with abnormal fetuses is only one in five.

Others factors not rigidly controlled in this experiment have been examined. Nutrition and handling have been relatively uniform in both the

test and control animals. The inocula (virus and TCF) used in this experiment were tested prior to use and were found to be free of contaminating viral agents; except for very small amounts of antibiotics (100 γ of penicillin and 100 units of streptomycin per ml.), the inocula had no known teratogenic chemical agents. There was nothing unusual about the passage history of the virus inoculum (14th passage in tissue culture) employed. However, the virus used in these studies has not been adapted by repeated passages to the experimental animal under study.

The type of abnormalities were strikingly similar in the rubella inoculated group and the TCF inoculated group, and included exencephaly, cervical spina bifida, and cleft lip and palate which were common to both groups. The only fetal abnormality in the uninoculated group was a case of cleft palate.

The role of seasonal variation on the congenital abnormality and resorption rates does not seem to be critical since the mothers with abnormal babies were randomly distributed throughout the year. The possibility that a genetic factor alone or in combination with other factors had played a key role in the results of this study cannot be determined from the present data.

This study did not show that rubella virus was the cause of the fetal deaths and congenital abnormalities in the ferret under the conditions of our experiment. A variable or variables not knowingly introduced in the experiment could have played the major teratogenic role. There is no specific information available to indicate that any or all of the above factors were dominant in these studies.

Summary and Conclusions

The possible teratogenic effect of rubella virus in the ferret model system was studied. The data presented did not show a clear, unequivocal evidence for this role. There was no significant and consistent reproducibility of abnormalities and resorptions in the test animals compared to the controls in seven experimental trials. Variations in the frequency of the phenomenon were noted in the same experimental group of animals at different times. The cause or causes for these differences are not clear; a number of variables were considered.

References

1. Fabiyi, A., Gitnick, G. L., and Sever, J. L.: Chronic Rubella Virus Infection in the Ferret (*Mustela putorius furo*) Puppy, *Proc Soc Exp Biol & Med*, 125:766-771, 1967.
2. Fabiyi, A., Elizan, T. S., and Sever, J. L.: Unpublished data.
3. Rorke, L., Fabiyi, A., Elizan, T. S., and Sever, J. L.: Experimental and Cerebrovascular Lesions in Congenital and Neonatal Rubella-Virus Infection of Ferrets, *The Lancet*, 2:153-154, 1968.

Received for publication September 11, 1968

Study of Rubella Virus as a Teratogen in Experimental Animals: A Short Review†

TERESITA S. ELIZAN, M.D.,* AKINYELE FABIYI, PH.D.,* AND
JOHN L. SEVER, M.D., PH.D.

Present interest in rubella as a teratogen dates from Gregg's classical paper in 1941 (1) in which he evaluated the results of a rubella epidemic in Australia during 1940. He found that 68 out of 78 infants with congenital cataract were born of mothers who had contracted rubella early in their pregnancy.

Early retrospective estimates (2, 3) of fetal damage after maternal rubella in the first trimester of pregnancy ranged as high as 80 to 90 per cent; since 1950, however, a downward revision of estimates of the risk of congenital malformations has resulted from more complete retrospective and prospective investigations (4-8). Approximately 20 per cent of live born infants of mothers who had rubella in the first trimester of pregnancy will have malformations (9-11). The spontaneous abortion rate in this same maternal group is estimated to be 10 to 15 per cent (12). The decline in frequency of congenital defects with increasing gestational age at onset of maternal rubella is reportedly not distinct until the beginning of the second trimester (13).

In the congenital rubella syndrome, the fetus is infected and remains so for prolonged periods of time after birth (14). The syndrome can also occur in infants born of mothers who, although infected as shown by serological methods, had no apparent or clinical disease. There is some evidence that reproductive failure may be induced when rubella occurs at times other than the first trimester of pregnancy (11). The major fetal effects of maternal rubella are well known and they include cataract, glaucoma, patent ductus arteriosus, peripheral pulmonic stenosis, microcephaly, perceptive deafness, and mental retardation.

Although there has long been experimental evidence indicating a viral etiology of rubella (15, 16) characterization of the causative agent was accomplished only in 1962 with the dual independent reports of isolation of rubella virus by Parkman, Buescher, and Artenstein (17), and by Weller and Neva (18). Since then, there has been a recognized need for a susceptible experimental animal host for the study of congenital and neonatal rubella virus infection.

From the Section on Infectious Diseases, Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

* Present address: Department of Neurology, Laboratory of Neurovirology, The Mount Sinai School of Medicine, New York, New York 10029.

† Presented at the Eighth Annual Meeting of the Teratology Society, at Buck Hill Falls, Pa., on May 15-17, 1968.

Experimental Animal Studies in the Literature

Monkeys (Macaca mulatta): In 1965, Parkman et al (19), reported that the rhesus monkey was a sensitive, susceptible host for studying experimental rubella infection, and that the pattern of virus excretion and antibody response was similar to that observed in human rubella, although simian infection was clinically inapparent. Antibody persisted for at least 10 months and was protective against virus challenge. The authors demonstrated placental transmission of rubella virus in pregnant monkeys infected early in gestation (20). Recovery of the virus from the fetuses was obtained in 3 of 6 animals inoculated intravenously during their fourth week (28 days) of gestation, an equivalent stage of gestation as the first trimester in human; virus recovery attempts were negative on tissue of two other animals infected during the nineteenth week (133 days) of gestation, which is comparable to the last trimester in man. There was no evidence of abnormality in the embryos and fetuses; size and anatomical development were consistent with gestational age.

Sever et al (21), inoculated rubella virus intravenously into 5 pregnant monkeys at 25 to 28 days' gestation, and found no evidence of infection, congenital malformation, petechia, or hepatosplenomegaly in the 4 live offspring studied. Transplacental antibody was present in cord blood at birth.

Recently Delahunt and Rieser (22), inoculated rubella virus by intravenous, intramuscular, and/or intranasal routes into 14 pregnant monkeys when the embryos were 20 to 44 days old. Nine females inoculated at 21 to 28 days' gestational age aborted with loss of conceptus which was not further studied. The 5 viable fetuses that were recovered by Caesarian sections between 56 to 133 days of gestation were reported to have had significant reduction in fetal size. Two of the fetuses inoculated at 20 to 26 days, respectively, had lenticular changes on light microscopic examination of the eyes; no other pathological changes were noted; virus was isolated from the fetal spleen, liver, and brain of the second fetus. The 3 fetuses inoculated at 31, 33, and 44 days had essentially normal eyes on light microscopy; electron microscopy of 2 of these apparently revealed "occasional virus-like particles in the lens capsule," and "dark electron-dense material in the lens epithelium;" petechial hemorrhages on the chest, face and trunk, a swollen fetal liver, and histologic defects of the ears, bones, and chorion were also briefly described in this latter group of fetuses. Two fetuses of untreated mothers were used as controls in the study. Compared to a spontaneous abortion rate of 15 to 20% in the author's primate breeding colony, their rubella teratogenic investigation had a rate of 60%, an increase that was considered another sequela of virus inoculation.

Baboons (Papio leucephaeus): Hendricks (23) conducted a rubella teratogenic study in the baboon by inoculating 6 pregnant animals at 23 and 98 days' postconception. There were 3 abortions, 1 fetal death, and 2 neonatal deaths. No congenital defects were reported.

Hamsters (Mesocricetus auratus): Oxford and Schild (24) reported the

multiplication of 2 strains of rubella virus in the golden hamster, but failed to demonstrate transplacental passage of rubella in 25 animals inoculated intranasally at various stages of gestation.

Rats: Cotlier et al (25) and Bohigian et al (26) using the same data, recently reported a series of experiments on pregnant albino rats (species unspecified) inoculated intramuscularly with rubella virus on the fifth or sixth day of a 21-day pregnancy period. Infected animals were sacrificed on the fifteenth day of pregnancy, or were allowed to deliver and the newborn sacrificed during the first day of life. The authors reported the following clinical signs in the offspring of rubella-inoculated mothers: marked decrease in size and weight (20 to 40% of that of controls), radiographic alterations of retarded bone growth, cachexia, cyanosis, purpura, lenticular opacities, open fontanellas, and missing hind limbs. There was apparently a high incidence of neonatal deaths. Pathological changes included markedly thin and atrophic intraventricular septum and disrupted cords of cardiac muscle; destruction, necrosis and vacuolation of the crystalline lens, with "viral-like particles among the nuclear debris" on electron microscopy. Rubella virus was reportedly identified by the indirect immunofluorescent technique in the developing fetal lens fibers and epithelium, in the retina, and in the heart tissue of infected rats. The tissue controls used in the immunofluorescent studies were not discussed. There were no spontaneous malformations described for the control animals.

Comments

The paucity of data on rubella virus as a teratogen in experimental animal models is obvious from this review. The positive findings of Delahunt and Reiser (22), Cotlier et al and Bohigian et al (25, 26), have not been confirmed by other investigators to date. The difficulties of interpreting the results of such teratogenic studies are exemplified by our own experience in the ferret model as reported in the preceding article (27). Many factors have to be analyzed and prospectively controlled before a meaningful relationship can be drawn between rubella virus as a teratogenic agent and an experimental animal host. Species of the animal used, control of its genetic background, baseline data on the frequency of spontaneously occurring abnormality rate in the source colony at various seasonal times of the year, and the timing, degree, and frequency of maternal infection, placental transfer, and subsequent fetal infection, are some of the important variables to consider. Other factors include possible effects of nutrition, handling and manipulations inherent in experimental trials, virus passage history and species-adaptation, presence of contaminating teratogenic agents in the inoculum and adequacy of control animals. None of the reported experimental studies cited above adequately controlled most of these factors.

References

1. Gregg, N. M.: Congenital Cataract following German Measles in the Mother, *Tr Ophth Soc Australia* 3:35-46, 1944.
2. Swan, C., H. L. Tostevin, B. Oraare, H. Mayo, and G. H. B. Black: Congenital De-

fects in Infants following Infectious Disease during Pregnancy, *MJ Australia* 2:201-220, 1943.

3. Wesselhoef, C.: Medical Progress: Rubella (German Measles) and Congenital Deformities, *NEJ Med* 240:258-261, 1949.
4. Lundstrom, R.: Rubella during Pregnancy, *Acta Paediat* 41:583-594, 1952.
5. Ingalls, T. H., and N. Purshottam: Fetal Risks from Rubella during Pregnancy, *NEJ Med* 249:454-455, 1953.
6. Greenberg, M., O. Pellitteri, and J. Barton: Frequency of Defects in Infants whose Mothers had Rubella during Pregnancy, *JAMA* 165:675-678, 1957.
7. Michael, R. H., and G. W. Mellin: Prospective Experience with Maternal Rubella and the Associated Congenital Malformations, *Pediat* 26:200-209, 1960.
8. Tartakow, I. J.: The Teratogenicity of Maternal Rubella, *J Pediat* 66:380-391, 1965.
9. Manson, M. M., W. P. D. Logan, and R. M. Loy: Rubella and Other Virus Infections during Pregnancy, Reports on Public Health and Medical Subjects, No. 101, Ministry of Health, London, Her Majesty's Stationery Office, London, 1960.
10. Lundstrom, R.: Rubella during Pregnancy. A Follow-up Study of Children Born after an Epidemic of Rubella in Sweden, 1951, with Additional Investigations on Prophylaxis and Treatment of Maternal Rubella, *Acta Paediat* (Uppsala), 51 (Suppl. 133) 1-110, 1962.
11. Medearis, D. N., Jr.: Comparative Aspects of Reproductive Failure Induced in Mammals by Viruses, *In* K. Benirschke (Ed.): Proceedings of Conference on Comparative Aspects of Reproductive Failure, Dartmouth Medical School, 1966. New York, Springer-Verlag, pp. 333-349, 1967.
12. Weller, T. H., C. A. Alford, Jr., and F. H. Neva: Changing Epidemiologic Concepts of Rubella, with Particular Reference to Unique Characteristics of the Congenital Infection, *Yale J Biol Med* 37: 455-467, 1965.
13. Heggie, A. D.: Intrauterine Infection in Maternal Rubella, *J Pediat*, 71:777-782, 1967.
14. Alford, C. A., Jr., F. A. Neva, and T. H. Weller: Virologic and Serologic Studies on Human Products of Conception after Maternal Rubella, *NEJ Med* 271:1275-1281, 1965.
15. Habel, K.: Transmission of Rubella to Macacus Mulatta Monkeys, *Public Health Rept* 47:1126-1139, 1942.
16. Anderson, S. G.: Experimental Rubella in Human Volunteers, *J Immunol* 62:29-40, 1949.
17. Parkman, P. D., E. L. Buescher, and M. S. Artenstein: Recovery of Rubella Virus from Army Recruits, *Proc Soc Exptl Biol & Med* 111:225-230, 1962.
18. Weller, T. H., and F. H. Neva: Propagation in Tissue Culture of Cytopathic Agents from Patients with Rubella-like Illness, *Proc Soc Exptl Biol & Med* 111:215-225, 1962.
19. Parkman, P. D., P. E. Phillips, R. L. Kirschstein, and H. M. Meyer, Jr.: Experimental Rubella Virus Infection in the Rhesus Monkey, *J Immunol* 95:743-752, 1965.
20. Parkman, P. D., P. E. Phillips, and H. M. Meyer, Jr.: Experimental Rubella Virus Infection in Pregnant Monkeys, *Amer J Dis Child* 110:390-394, 1965.
21. Sever, J. L., et al: Experimental Rubella in Pregnant Rhesus Monkey, *J Infect Dis* 116:21-26, 1966.
22. Delahunt, C. S., and N. Rieser: Rubella-induced Embryopathies in Monkeys, *Amer J Obst & Gynec* 99:580-588, 1967.
23. Hendricks, A. G.: Teratological Findings in a Baboon Colony, FDA Conference on Nonhuman Primate Toxicology, Airlie House, Virginia, 1966.
24. Oxford, J. S., and G. C. Schild: Growth of Rubella Virus in the Hamster (*Mesocricetus auratus*), *Virology* 28:780-782, 1966.
25. Cotlier, E., et al: Pathogenic Effects of Rubella Virus on Embryos and Newborn Rats, *Nature* 217:38-40, 1968.

26. Bohigian, G. M., J. Fox, and E. Cotlier: Immunfluorescent Localization of Rubella Virus in the Lens, Retina, and Heart of Congenital Rubella-infected Rats, *Amer J Ophthal* 65:196-201, 1968.
27. Elizan, T. S., Fabiyi, A., and Sever, J. L.: Experimental Teratogenesis in Ferrets using Rubella Virus, *J Mount Sinai Hosp* 36:103-107, March-April 1968.

Received for publication September 11, 1968

Hypokalemia, Metabolic Acidosis, and Hypocalcemic Tetany in a Patient Taking Laxatives

A Case Report

PAUL GOLDFINGER, M.D.*

Introduction

Electrolyte alterations in chronic laxative users have been well described (1-5). Very often such patients are psychiatrically disturbed, taking excessive amounts of laxatives. The case reported here is that of a 61-year-old woman with a marked electrolyte imbalance, probably due to laxative abuse. Of particular interest was the presence of severe hypocalcemia thought to be secondary to excessive phosphate ingestion. The physiologic mechanisms are discussed, especially with reference to the hypocalcemia.

M.G. (MSH #229211), a 61-year-old white female secretary, was admitted to the hospital on March 11, 1968, because of carpopedal spasm of one day's duration. The patient had been in good health most of her life except for a history of psychiatric problems dating back over thirty years. She underwent a spinal fusion in 1955 because of a slipped disc, and in 1963 was admitted to the psychiatric service because of extreme anxiety and barbiturate addiction.

On the day prior to admission she noted "deformity" of her hands and feet associated with paresthesias. In the emergency room on March 11 she was found to have carpopedal spasm with positive Chvostek and Trousseau signs. On admission she appeared as a pale woman with a flattened affect. She responded to questions slowly, with short, bland answers. The skin was dry, and a few bibasilar rales were heard over the chest and cleared with deep inspiration. The pulse was 68, respirations 14, and temperature 99.4. Blood pressure was 120 systolic, 70 diastolic. Admission chemistries included urea nitrogen 39 mg%, sodium 146 mEq, potassium 3 mEq, chloride 91 mEq, and carbon dioxide 14 mEq per liter. The calcium was 4 mg and the phosphorous was more than 10 mg%. Magnesium was 1.8 mg%. An Astrup analysis done on arterial blood showed a pH of 7.25, actual pCO₂ 27 mm Hg, base excess minus 14.3 mEq per liter blood, standard bicarbonate 14.1 mEq per liter plasma, actual bicarbonate 11.5 mEq per liter plasma, total CO₂ 12.3 mEq per liter plasma and buffer base of 35 mEq per liter blood. Urinalysis revealed a pH of 5, specific gravity 1.012, no albumin or sugar, and a negative Sulkowitch test. Urinary pH repeated with the Astrup technique was 4.85. The hemoglobin was 12.7 gm% with a white count of 19,100 (74 polys, 16 bands, 3 lymphocytes, and 7 monocytes). Erythrocyte sedimentation rate was 21 mm per hour. Parathyroid hormone concentration (6) was measured by Drs. R. S. Yalow and S. A. Berson and found to be elevated.

Admission electrocardiogram showed left axis deviation plus a prolonged QT interval. The patient was treated with intravenous saline solutions containing potassium chloride and calcium gluconate for twenty four hours. Her electrolytes rapidly returned to normal levels. On March 12 urea nitrogen was 28 mg%, sodium 138 mEq, potassium 4 mEq, chloride 109 mEq, and carbon dioxide 22.5 mEq per liter. Calcium was 11.9 mg%. On March 13, the calcium rose to 14 mg with a phosphorous of 4.2 mg%, and all supplemental electrolytes were discontinued. On March 14 the calcium fell to 10.4 and the phosphorous to 2.4 mg%. At this time, the patient admitted to the chronic use of bisacodyl laxative

* Assistant Resident, the Department of Medicine, The Mount Sinai Hospital, New York, N.Y.

tablets, Fleets enemas (sodium biphosphate and sodium phosphate), and oral Fleets phosphosoda (each 100 cc had 48 gm sodium biphosphate and 8 gm sodium phosphate). She denied excessive use of these medications, but admitted to taking at least two bisacodyl tablets per day and having between one and four bowel movements per day. She also admitted to "occasional" use of the phosphate compounds.

On March 17 she had a grand mal seizure lasting four minutes, with a transiently positive left Babinski. Serum calcium at this time was 9.6 mg, while the cerebrospinal fluid calcium was normal at 4.8 mg%. She was not alkalotic at this time, nor was she receiving any bicarbonate. Electroencephalogram showed bilateral dysfunction and the brain scan was normal. The skull films were normal and there were no intracranial calcifications. A neurologic evaluation was obtained, but there was no definite explanation for the seizure.

On April 2, the day prior to discharge, after 21 days off electrolyte supplements, her urea nitrogen was 11 mg%, creatinine 1.1 mg%, sodium 145 mEq, chloride 115 mEq, and carbon dioxide 25 mEq per liter. The calcium was 9.1 and the phosphorous 3.6 mg%. A repeat parathormone assay was done and found to be normal.

Twenty-four hour urine calciums were obtained at various times after the electrolyte imbalance had been corrected. On March 14 it was 174 mg and on March 21 it was 144 mg. On March 22 the patient was taken off the regular hospital diet and begun on a Bauer Aub diet. Twenty-four hour calciums done on March 26 and 27 were 80 and 68 mg% respectively. On March 28, the patient was begun on a five day course of phosphosoda (12 cc p.o. per day) in an attempt to reproduce the hypocalcemia. The serum electrolytes were not, however, altered by this therapy. Followup urinalyses showed specific gravities ranging 1.004 to 1.012, colony counts of less than 1000, and twenty-four hour urine protein of less than .01 gm per liter. Subsequent to the admission elevation, all white blood counts were normal. A fasting blood sugar was 90 mg%. Alkaline phosphatase was elevated early in the hospitalization (105 and 140 International Units) with a subsequent drop to a normal of 85 units at time of discharge. Thyroid and adrenal function tests were normal, as was the thyroid scan. A bone survey showed no abnormalities other than spinal fusion from prior surgery. Intravenous pyelogram revealed a calcific density in the superior calyx of the left kidney. Barium enema showed diverticulae, and an upper gastrointestinal series with small bowel follow through was reported as normal. On May 19, forty-six days after discharge, the patient's serum calcium was 9.2 with a phosphorous of 4 mg%.

Discussion

The entire electrolyte derangement in this case can be explained on the basis of purgative abuse. The first important paper on this topic was presented by Schwartz and Relman (3) who reported two cases of chronic potassium depletion from overuse of laxatives. In following years, other papers appeared describing similar phenomena, including acid base imbalances, impaired renal function, tetany, hypomagnesemia, and hypocalcemia. In 1962 Staffurth and Allott (1) described a case of chronic purgation that had paralysis, tetany, hypokalemia, hypocalcemia, and severe metabolic acidosis. They attributed the hypocalcemia to parathyroid hypoactivity secondary to kaliopenic damage to the gland. However, this hypothesis was purely speculative.

Although there are not many conditions which produce hypocalcemia with hyperphosphatemia (7), the cause in our patient was not readily apparent. Hypoparathyroidism was excluded by the elevated parathormone concentration, and pseudohypoparathyroidism was ruled out by the absence of characteristic physical signs. The patient did not have chronic renal insufficiency, and excessive losses of calcium in the stool due to diarrhea were excluded by

the elevated serum phosphorous, by the absence of malabsorption, and by the lack of radiologic signs of calcium mobilization from bone.

The most likely, although unproved, explanation was that excessive use of phosphates produced the hyperphosphatemic hypocalcemia. It is supported by the history of chronic purgative use, by the coincident acid base imbalance characteristic of laxative abuse, by the rapid response to therapy, and by the maintenance of a normal serum calcium without supplements for over two months after admission. The inability to reproduce hypocalcemia in this patient by giving phosphosoda was inconclusive because of the small doses used and the short duration of treatment.

Intravenous and oral phosphates have been used successfully in the treatment of hypercalcemia (8, 9). They lower serum calcium by deposition of calcium phosphate salts, probably in bone, and perhaps in other tissues. Urinary calcium decreases with phosphate therapy (9), so that normal renal function is not required for the successful lowering of serum calcium with phosphate (10, 11). The oral phosphates lower calcium more gradually than by the intravenous route (10) and have an additional mechanism of action by binding calcium in the stool.

Goldsmith and Ingbar (9) point out that marked hyperphosphatemia is unusual in the phosphate therapy of hypercalcemia, but they did not measure the maximum rise in serum phosphorous during infusion. Carey (12) recently reported a case of hypercalcemia in which serum phosphorous rose to 14.4 mg% while on oral phosphate therapy. Bartter (7) lists excessive phosphate ingestion as a cause of hypocalcemia with hyperphosphatemia. The transient prerenal azotemia which this patient had may have contributed to the magnitude of the phosphorous rise.

The transient elevation in parathormone was probably a normal physiologic response to the hypocalcemia, i.e., secondary hyperparathyroidism (13, 14). Acidosis tends to delay recovery from hypocalcemia by inhibition of parathormone (15), but this mechanism was apparently of little importance in this case.

The cause of the metabolic acidosis and hypokalemia was probably loss of bicarbonate and potassium in the stool due to purgative abuse (16). The tendency for alkalosis to accompany hypokalemia in such a situation is often masked by the bicarbonate loss. In fact, there is some danger of hyperkalemia if potassium is given too fast, since cells accept potassium much less readily in the presence of acidosis (16). There is also a danger of seizures if large amounts of bicarbonate are given for acidosis in the presence of hypokalemia. It is of interest that the patient became tetanic despite the protective effect of the acidosis. On the other hand, hyperphosphatemia will increase neuromuscular irritability and may decrease calcium ionization (17).

The normal magnesium was of interest because it has been shown that in some patients with hypomagnesemia and hypocalcemia, the serum calcium may not respond to calcium therapy, but that both abnormalities may be corrected by magnesium (18, 19). Magnesium deficiency interferes with cal-

cium release from bone, and by correcting the hypomagnesemia in such cases, the mobilization of calcium into serum is increased (18).

Summary

A case is reported of a patient on chronic laxative therapy in whom hypokalemia, metabolic acidosis, and hypocalcemic tetany developed. The diagnostic and physiologic considerations are discussed, particularly with reference to the hypocalcemia.

References

1. Staffurth, J. S., and Allott, E. N.: Paralysis and Tetany due to Simultaneous Hypokalemia and Hypocalcemia with Other Metabolic Changes, *Am J Med* 33:800, 1962.
2. Pereira, V. G., et al: Electrolyte and Renal Changes in Severe Potassium Depletion, *Metabolism* 14:800, 1965.
3. Schwartz, W. B., and Relman, A. S.: Metabolic and Renal Studies in Chronic Potassium Depletion Resulting from Overuse of Laxatives, *J Clin Invest* 32:258, 1953.
4. Litchfield, J. A.: Low Potassium Syndrome Resulting from the Use of Purgative Drugs, *Gastroenterology* 37:483, 1959.
5. Fourman, P.: The Tetany of Potassium Deficiency, *Lancet* 2:525, 1954.
6. Yalow, R. S., and Berson, S. A.: Labeling of Proteins—Problems and Practices, *Trans New York Academy of Sciences* 28:1033, 1966.
7. Bartter, F. C.: Parathyroid Gland in the *Textbook of Medicine*, ed. by Beeson and McDermott, W. B. Saunders, Co., Philadelphia, Pa., 1967, p. 1363.
8. Massry, S. G.: Inorganic Phosphate Treatment of Hypercalcemia, *Clinical Research (abstr.)* 16:129, 1968.
9. Goldsmith, R. S., and Ingbar, S. H.: Inorganic Phosphate Treatment of Hypercalcemia of Diverse Etiologies, *New Eng J Med* 274:1, 1966.
10. Shackney, S., and Hasson, J.: Precipitous Fall in Serum Calcium, Hypotension, and Acute Renal Failure after Intravenous Phosphate Therapy for Hypercalcemia, *Ann Int Med* 66:906, 1967.
11. Better, O.: Phosphate for Hypercalcemia, *Ann Int Med* 67:1349, 1967.
12. Carey, R. W., et al: Massive Extraskkeletal Calcification during Phosphate Treatment of Hypercalcemia, *Arch Int Med* 122:151, 1968.
13. Sherwood, L. M.: Relative Importance of Parathormone and Thyrocalcitonin in Calcium Homeostasis, *New Eng J Med* 278:663, 1968.
14. Rosenbaum, J. L.: Sudden Hypocalcemia in the Normal Man, *J Clin Endo* 25:767, 1965.
15. Fujita, T., et al: Effect of Acidosis and Alkalosis on Recovery from Hypocalcemia, *Endocrinology* 76:1202, 1965.
16. Doe, R. P.: Metabolic Acidosis—Nondiabetic, *Arch Int Med* 116:717, 1965.
17. Paschkis, K. E., et al.: *Textbook of Clinical Endocrinology*, 3rd Ed., Harper and Row, Co., N.Y. 1967, p. 918.
18. Fourman, P.: Magnesium Deficiency and Hypocalcemia in Intestinal Malabsorption, *Lancet* 2:51, 1965.
19. Clarke, P. C.: Hypocalcemic, Hypomagnesemic Convulsions, *J Ped* 70:806, 1967.

Received for Publication September 16, 1968

Potassium Depletion and Metabolic Alkalosis in a Psychiatrically Disturbed Patient

A Case Report

PAUL GOLDFINGER, M.D.*

Introduction

Electrolyte alterations in psychiatrically disturbed patients may present diagnostic problems. Very often such patients have multiple sources of electrolyte loss (e.g., diuretics or laxatives) and they frequently conceal these from their physicians (1, 2). In such cases, the diagnosis may become one of exclusion.

The case described here is that of a 28-year-old woman with severe hypokalemic hypochloremic alkalosis, probably due to diuretic abuse. The mechanisms and therapeutic problems relating to diuretic induced electrolyte imbalance are discussed.

K.B. (MSH #444023), a 28-year-old white female secretary, was admitted to the hospital with the chief complaint of palpitations of two weeks' duration. For the six weeks prior to admission she had been troubled by painful, swollen gums for which she was under dental care. Associated with this were intermittent nausea and vomiting, as well as a ten pound weight loss. During the week before admission, her palpitations became more frequent, her vomiting increased, and she complained of dizziness and profound weakness. She was referred for admission because of an abnormal electrocardiogram. The patient's past history was negative except for an emotional upset at age twenty associated with depression, weight loss, and cessation of menses. Her menses resumed when she was treated with "pills and injections." Two months before admission she became pregnant and subsequently underwent an abortion. The patient, a former broad jumper, was European born, widely traveled, and single. She smoked more than one pack of cigarettes per day and she denied taking any drugs.

On admission the patient was thin, pale, and appeared depressed. The temperature was normal, the radial pulse 90, and the respirations 16. The blood pressure was 100 systolic, 75 diastolic. Her skin was dry and her eyes were somewhat sunken. There was moderately severe pyorrhea with marked gingival irritation. A Grade II systolic ejection murmur was audible over the second left intercostal space, left sternal border. The rhythm was irregular, characterized by a premature contraction every third beat, with a pulse deficit of 3:2. No edema or physical deformities were present.

Admission electrocardiogram showed a prolonged QT interval, trigeminy, and peaked P waves. The hemoglobin was 16.7 gm%, and the white count was 8600 with a normal differential. The serum sodium concentration was 131 mEq, the potassium 1.9 mEq and the chloride 56 mEq per liter. An Astrup analysis of arterial blood revealed a pH of 7.55, actual pCO₂ of 65 mm Hg, base excess of plus 20 mEq per cc blood, standard bicarbonate of 48.5 mEq per liter plasma, and actual bicarbonate of 56 mEq per liter of plasma. Blood urea nitrogen equalled 34, magnesium 1.9 and uric acid 10.4 mg%. An oral glucose tolerance test done early in her admission showed a one hour sugar of 236 with a two hour level of 100 mg%.

Because of the severe hypokalemic hypochloremic alkalosis and the trigeminal rhythm,

*Assistant Resident, the Department of Medicine, the Mount Sinai Hospital, New York, N.Y.

treatment was begun immediately with intravenous saline solutions containing large amounts of potassium chloride. The ventricular prematures quickly disappeared, and blood chemistries soon returned to normal range.

Urea nitrogen fell to 11 mg with a creatinine of .8 mg%, and the uric acid decreased to 4 mg%. For the first week of her admission, the patient was producing dilute urines with specific gravities of 1.002 to 1.006. By the tenth day of her hospitalization, she was capable of concentration from 1.016 to 1.020. Her urine pH was fixed at 5, regardless of changes in serum pH.

It soon became apparent that the patient had a severe deficit of total body potassium. Although giving large amounts of potassium chloride corrected the serum electrolyte values, discontinuing the supplements resulted in rapid recurrence of the hypokalemic alkalosis. In addition, a prolonged hospitalization became necessary when it was found that therapeutic doses of potassium chloride given by mouth produced intolerable nausea and vomiting.

Despite the significant potassium deficit in this patient and the need for continuous potassium supplementation, her urinary potassium excretion remained quite high. For example, on the tenth hospital day, with a serum potassium of 3 mEq per liter and a potassium intake of 180 mEq, she excreted 111 mEq of potassium in twenty-four hours.

A urinary aldosterone level, obtained early in her admission, at a time when she was normokalemic on supplements, was found to be within normal limits. Twenty-four hour urinary 17-hydroxy and 17-ketosteroids were normal.

After nearly two months on oral and intermittent intravenous potassium supplements, she was transferred to the Clinical Research Center where the supplements were stopped and she was placed on a calculated diet of 9 gm sodium chloride and 2.3 gm potassium. Total body potassium was determined and found to be 46 mEq per kilogram with a normal of 41 mEq per kilogram by a whole body counting technique. On this diet, she maintained her serum potassium at $3.8 \pm .7$ mEq per liter. Her serum sodium ranged between 135–144 mEq and her chloride between 90–102 mEq per liter. Creatinine clearance was 76.1 cc per minute. Twenty-four hour urine potassium averaged 32.9 ± 6.8 mEq and the sodiums varied between 84 and 166 mEq. Serum pH was 7.438 and urine pH was 5 to 6. A five day stool collection revealed an average daily potassium loss of 13 mEq. An intravenous pyelogram was normal. Further metabolic studies were not done due to lack of patient cooperation.

Since the admission history did not adequately explain the cause of the severe electrolyte derangement, additional information was obtained in fragments by various interviewers. The patient admitted to taking 10–16 Fiorinal tablets (containing phenacetin) per day for one year for severe headaches until six months before admission. After that she took 14–16 Vanquish tablets (APC) per day plus numerous aspirin. She also admitted to taking a Dexedrine compound for "drowsiness." In addition, in her handbag, she carried a bottle of hydrodiuril which she took for occasional mild ankle swelling "no more than once per month." To another interviewer she said she took hydrodiuril once per week. A psychiatric consult described "significant psychopathology with chronic underlying depression plus a considerable tendency to evade, elaborate, and exaggerate."

A neurologic evaluation was obtained, and the headaches were considered to be of a mixed tension and migraine type. Skull films, electroencephalogram, and brain scan were all normal. She was discharged with a potassium of 3.2 mEq per liter.

Discussion

Although the patient admitted to the use of thiazides, she did not admit to using amounts sufficient to cause the clinical picture. The metabolic studies, however, proved that there were no primary renal, adrenal, or gastrointestinal potassium wasting defects. The initial hyperuricemia and abnormal glucose tolerance test support the theory that she sustained her hypokalemic hypochloremic alkalosis as a result of thiazide abuse. The electrolyte disturbance

was further complicated by anorexia, nausea and vomiting, which are well known effects of metabolic alkalosis (3).

The thiazides are thought to produce hypokalemia by two mechanisms. The first is by increasing the amount of sodium presented to distal nephron sodium-potassium exchange sites. The second is by a carbonic anhydrase inhibitory effect which decreases tubular secretion of hydrogen ions and therefore secondarily increases distal sodium-potassium exchange. This latter mechanism is of little practical importance, since large doses of thiazides are required for carbonic anhydrase inhibition to be significant (4). Secondary aldosteronism may occur (1) as a result of sodium depletion and/or extracellular fluid volume contraction. This may help perpetuate the hypokalemia.

Some authors have pointed out that the kaluresis which occurs at the beginning of thiazide therapy becomes less pronounced as treatment is continued. They suggest that the hypokalemia may be due to altered intra-extracellular potassium concentration gradients and not to a depletion of body potassium stores (5). Other work has shown that there is a true loss of total body potassium, and that this may occur even after a relatively short duration of thiazide therapy (6).

Besides hypokalemia, the other major metabolic alteration induced by thiazides is a hypochloremic alkalosis. There is some evidence to suggest that this alkalosis is the primary defect, and that the hypokalemia is a secondary phenomenon (5, 7). Alkalosis per se, regardless of total body potassium content, will lower serum potassium by .5 mEq per liter for each .1 rise in pH (8). This is primarily due to transfer of potassium ions into cells as hydrogen moves out (9). In addition, recent work has shown that repair of alkalosis can be accomplished without giving potassium (10). Schwartz has stressed the role of chloride therapy (11), and his and other works have demonstrated the correction of metabolic alkalosis with saline alone, despite large potassium deficits (10, 12). This latter situation is to be contrasted with the cases of "saline resistant alkalosis" in which potassium must be given before the alkalosis is corrected (10, 13). This is seen in Cushing's syndrome and in primary aldosteronism and represents a special mechanism in which the low potassium has caused an increased threshold for the tubular resorption of bicarbonate (13).

There are a number of related factors which interact to cause thiazide induced alkalosis (14). The thiazides act somewhere in the distal tubule to block reabsorption of salt and water (15, 16). This increases the supply of sodium to the more distal sites where enhanced ion exchange occurs. The total effect of this is to cause loss of hydrogen, potassium, sodium, and chloride in the urine, and to increase the resorption of bicarbonate. It has been found that the urinary losses of chloride are in excess of sodium (4). Since chloride is the only reabsorbable anion, excess losses of chloride cause the kidney to compensate in an effort to retain sodium (11). The effect of this is to further augment distal exchange mechanisms, thereby causing further urinary loss of potassium and hydrogen ions, increased bicarbonate re-

absorption, and continued production of an acid urine despite the alkalosis. This may explain the value of chloride therapy in this condition.

Other factors involved in perpetuating the alkalosis include potassium depletion per se (3, 17), secondary aldosteronism, and contraction of the extracellular space (12). This latter mechanism is important because it causes increased proximal tubular reabsorption (15) of salt, water, and bicarbonate, and thereby further deprives the distal tubule of needed chloride. It is the correction of this "third factor" effect which is thought to explain the beneficial use of saline in metabolic alkalosis (12).

The mild azotemia which this patient had was probably secondary to the severe alkalosis (3). In alkalosis-induced azotemia the urea nitrogen returns to normal when the acid base disturbance is corrected. This elevation in urea is not a contraindication to potassium therapy. A mild azotemia may also occur, however, with kaliopenic renal damage (13, 18). This patient may have had this entity, since there was an early inability to concentrate the urine (13) and a persistently acid urine despite the presence of alkalosis (19). The latter defect, however, was at least partially the paradoxical aciduria expected with diuretic induced alkalosis. Potassium wasting does not occur as part of the kaliopenic nephropathy (13). There was no evidence to suggest that she had a phenacetin nephropathy.

Primary aldosteronism was ruled out by the absence of hypertension, the normal aldosterone level when normokalemic, and the absence of potassium wasting off supplements. A renal biopsy was not done in this patient, however, her age, normal stature, and normal aldosterone make Bartter's syndrome (20) highly unlikely.

The presence of a trigeminal rhythm in this case is of interest because such arrhythmias are said to be rare in hypokalemia without digitalis (21). In Surawicz's cases of hypokalemia (22), however, every patient with a serum potassium of less than 2.6 experienced arrhythmias. One of these patients had ventricular premature contractions appearing in bigeminy. It is conceivable but unlikely that our patient was secretly taking digitalis. Therapy with potassium chloride was begun immediately in this patient because of the danger of ventricular fibrillation. Hypokalemia may also produce necrosis of the myocardium in man with permanent damage (23). Those who have studied such autopsy material urge rapid and complete reversal of hypokalemia.

The inability of this patient to tolerate satisfactory oral potassium chloride is consistent with the experience of Surawicz (24). 84% of his patients needed parenteral potassium chloride because of anorexia, nausea, or vomiting. Of particular interest in this patient were the large urinary potassium losses during repletion, and the long period of time required to replete her. The transfer of potassium into cells is quite slow. It takes fifteen hours for potassium to equilibrate as compared with two hours for water (17). Studies have shown that changes in urinary potassium during potassium depletion depend on the blood potassium and not on the total body potassium content

(18). Thus, giving large amounts of potassium chloride will cause increased urinary excretion as the body attempts to prevent extracellular fluid accumulation of potassium. Kaplan has pointed out that in potassium depleted patients, it may require 40 to 120 mEq per day for up to sixteen weeks to keep serum potassium normal (25).

Summary

A case is reported of a psychiatrically disturbed patient with potassium depletion and metabolic alkalosis, probably due to diuretic abuse. The etiology, physiologic, and therapeutic considerations are discussed, particularly with reference to diuretic induced electrolyte imbalance.

Acknowledgments

I thank Dr. Milton Brothers for permission to publish this case, Dr. James Robertson of Brookhaven National Laboratories for performing the total body potassium determination, and the staff of the Clinical Research Center for its assistance in the work up. The studies done were supported in part by an NIH grant ("General Multicategory Clinical Research Center—FR 71.")

References

1. Wolff, H. P., et al.: Psychiatric Disturbance Leading to Potassium and Sodium Depletion, Raised Plasma Renin Concentration and Secondary Aldosteronism, *Lancet* 1:257, 1968.
2. Editorial. Potassium Deficiency in Ambulant Patients, *Brit M J* 2:191, 1967.
3. Mulhausen, R. O., and Blumentals, A. S.: Metabolic Alkalosis, *Arch Int Med* 116:729, 1965.
4. Berliner, R. W.: Use of Modern Diuretics, *Circulation* 33:802, 1966.
5. Johansson, B., and Sievers, J.: The Effect on Serum Concentration of Sodium, Potassium and Chloride during Long-term Diuretic Therapy, *Angiology* 17:134, 1966.
6. Remenchik, A. P., et al: Depletion of Body Potassium by Diuretics, *Circulation* 33:796, 1966.
7. Rooth, G., and Furst, C: The Relation Between Hypopotassaemia and Alkalosis during Administration of Polythiazide and Chlorthalidone, *Acta Med Scand* 176:51, 1964.
8. Nuttall, F. Q.: Serum Electrolytes and Their Relation to Acid Base Balance, *Arch Int Med* 116:670, 1965.
9. Scribner, B. H., and Burnell, J. M.: Interpretation of the Serum Potassium Concentration, *Metabolism* 5:468, 1956.
10. Kassirer, J. P., and Schwartz, W. B.: Correction of Metabolic Alkalosis in Man without Repair of Potassium Deficiency, *Am J Med* 40:19, 1966.
11. Schwartz, Wm.: Pathogenesis and Replacement of Diuretic Induced Potassium and Chloride Loss, *Ann N Y Acad of Sci* 139:506, 1966.
12. Cohen, J. J.: Correction of Metabolic Alkalosis by the Kidney after Isometric Expansion of Extracellular Fluid, *J Clin Inves* 47:1181, 1968.
13. Schwartz, W. B., and Relman, A.: The Kidney in Potassium Depletion, *New Eng J Med*, 276:383, 1967.
14. Brest, A. N., and Moyer, J. H.: Clinical Pharmacology of Diuretic Drugs, *Am J Card* 17:626, 1966.
15. Hutcheon, D. E.: Recent Advances in the Pharmacology of Diuretic Drugs, *Am J Med Sci* 253:620, 1967.

16. Sullivan, L. P., and Pirch, J. H.: Effect of Bendroflumethiazide on Distal Nephron Transport of Sodium, Potassium, and Chloride, *J Pharm and Exper Ther* 151: 168, 1966.
17. Cantarow, A.: Potassium Metabolism. *Clinical Biochemistry*. W. B. Saunders, Philadelphia, Pa., 1962, Ch. 23.
18. Hamburger, J. W.: *Textbook of Nephrology*. W. B. Saunders, Co., Philadelphia, Pa., 1968, Chap. 12.
19. Hollander, W., Jr.: The Nephropathy of Potassium Depletion in the *Textbook of Renal Disease*, ed. by Strauss and Welt, Little, Brown and Co., Boston, Ch. 21.
20. Bartter, F. C.: Hyperplasia of the Juxtaglomerular Complex with Hyperaldosteronism and Hypokalemic Alkalosis, *Am J Med* 33:811, 1962.
21. Pick, A.: Arrhythmias and Potassium in Man, *Am Heart J* 72:295, 1966.
22. Surawicz, B., and Lepeschkin, E.: The Electrocardiographic Pattern of Hypopotassemia with and without Hypocalcemia, *Circulation*, 8:801, 1953.
23. McAllen, P. M.: Myocardial Changes Occurring in Potassium Deficiency, *Brit Heart J* 17:5, 1955.
24. Surawicz, B.: Clinical Manifestations of Hypopotassemia, *Am J Med Sci* 233:603, 1957.
25. Kaplan, N. M.: Hypokalemia in the Hypertensive Patient—Observations on the Incidence of Primary Aldosteronism, *Ann Int Med* 66:1079, 1967.

Received for publication September 16, 1968

Cerebellar Glioblastomas

SIDNEY W. GROSS, M.D., RICHARD COHEN, M.D., AND
SONGSANT PANICHA VANTANA, M.D.

Neurosurgeons and neurologists have learned unhappily that about half of all gliomas in adult life are rapidly growing malignant glioblastomas of the cerebral hemispheres.

These tumors have been known to pathologists for many years under various designations. Kaufmann (1911) was one of the first pathologists to have used the term "Spongioblastoma" in referring to this neoplasm. Later Globus and Strauss (1925) in a classic report "Spongioblastoma Multiforme" described this tumor in great detail and enumerated its essential characteristics. Bailey (1932) was never satisfied with the designation "Spongioblastoma Multiforme" for the malignant gliomas of the adult cerebral hemispheres. He pointed out that cells of this tumor rarely resemble spongioblasts of the developing nervous system and favored the term "Glioblastoma Multiforme" which he originally advocated (Bailey, 1930). Because of Bailey's preeminence as a student of brain tumors his lead was followed and "Glioblastoma" has remained as the term in almost universal favor.

Bailey and Cushing in their monograph "Tumors of the Glioma Group" (1926) referring to Spongioblastoma Multiforme state: "only two of 77 cases having been found in the cerebellum."

However, in Cushing's series of 2,023 brain tumors (1932) there were 862 gliomas, of these 208 were glioblastomas which "occurred without exception in the cerebral hemispheres of adults." Bailey, Buchanan, and Bucy reported several glioblastomas of the brain stem in children. None was primarily in the cerebellum.

In a paper concerning 102 brain tumors in children, Stern (1937) found two glioblastomas in the cerebellum, one in the pons, and one in the pons and cerebellum.

In our own experience we can not recall previously having seen a glioblastoma of the cerebellum. During the past year three such cases in adults came under our care.

Case Reports

CASE 1. A white housewife, age 49, complained of staggering, nausea, vomiting, and a bitemporal headache which began three months prior to admission. The past history was not relevant. In the hospital the patient preferred to lie in bed, refusing to move about because of discomfort. Blood pressure 130/80. There was horizontal nystagmus on looking to the right and a rotatory clockwise nystagmus on upward and downward gaze. Visual fields and fundi were normal. Babinski sign was positive on the right. There was marked ataxia of all limbs and she could not get out of bed to stand or walk. Complete laboratory

From the Department of Neurosurgery, Mount Sinai School of Medicine, New York, N.Y. 10029.

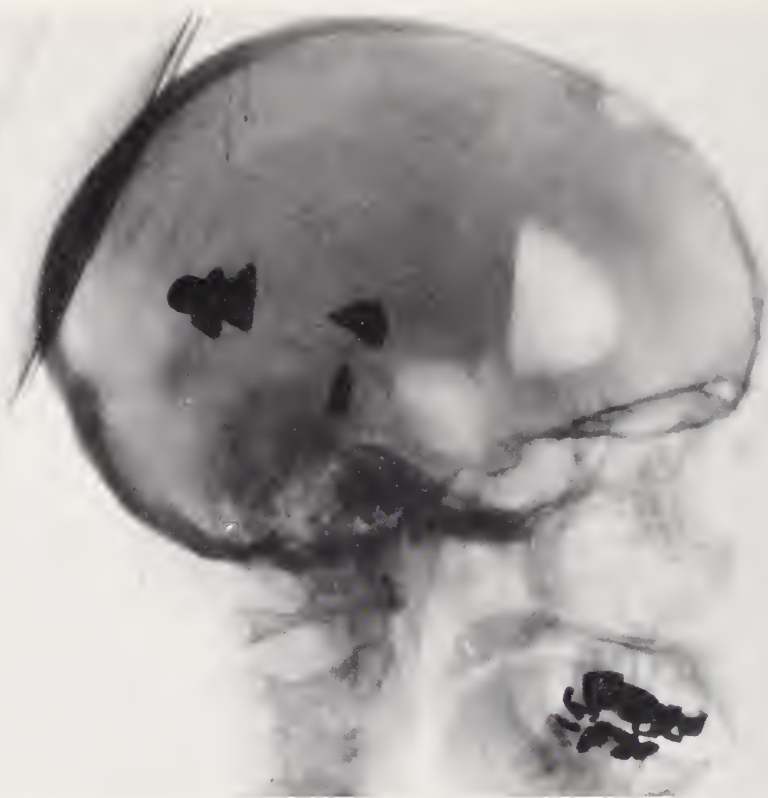


FIG. 1. Case 1. Pantopaque—air ventriculogram showing ventricular dilation and forward displacement of fourth ventricle.

survey for a primary extracerebral lesion was negative. The EEG disclosed bilateral cerebral dysfunction with marked accentuation in the right fronto-temporal area.

Angiography suggested moderate ventricular dilation. Lumbar air injection was done; however, air failed to fill the ventricles. A brain scan was normal. A ventriculogram with air and pantopaque showed ventricular dilation. The fourth ventricle was in the midline but displaced forwards (Fig. 1). Posterior fossa exploration uncovered a necrotic vascular mass in the superior vermis. In the first few days following surgery the patient improved. On the fifth postoperative day jaundice, fever, and stupor developed. From then on her course was downhill and in spite of aggressive postoperative management including tracheotomy she died 19 days after the operation. Only a surgical specimen was available for study. It consisted of two small firm grayish brown fragments which on microscopic study proved to be a glioblastoma multiforme (Fig. 2). The neoplastic cells were often multinuclear with cytoplasmic processes. Giant cells with bizarre hyperchromatic nuclei were numerous. Focal necrosis, mural hyperplasia of blood vessels, and marked pleomorphism characterized the tumor.

CASE 2. A white business man, age 64, complained of loss of appetite, nausea, vomiting, and weight loss of three months' duration. He had previously been well. Shortly before hospital admission he began to stagger and he complained of frontal and occipital headache.

On examination he appeared dull and weak. He could not stand unless supported. There was nystagmus on looking to the right and moderate incoordination in all limbs. Blood pressure 160/90. No systemic abnormalities were noted. The EEG showed bilateral cerebral

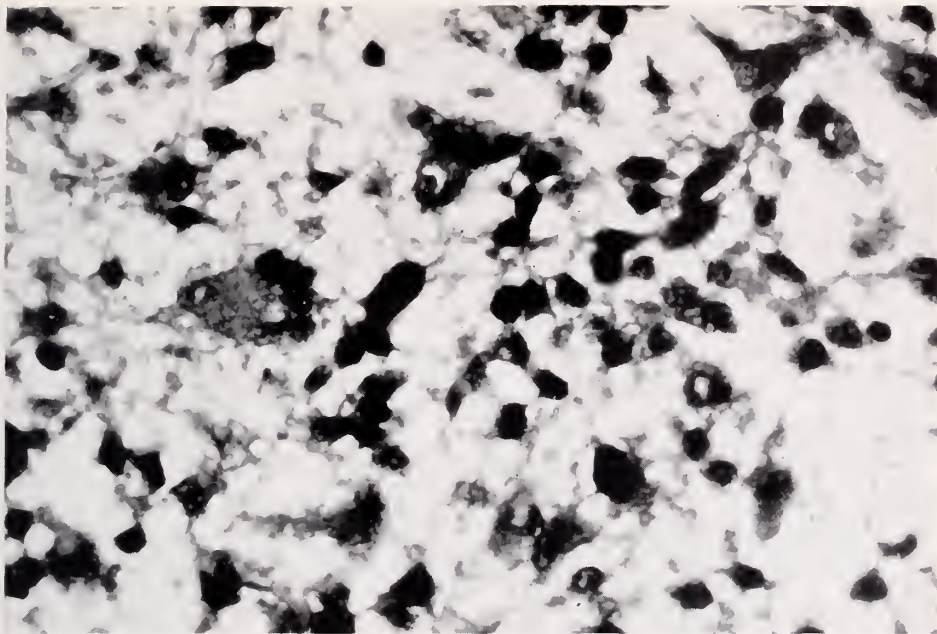


FIG. 2. Case 1. Photomicrograph showing multinucleated giant cells, pleomorphism, and microcystic change.

dysfunction. A left brachial angiogram showed a left cerebellar mass (Fig. 3). The patient's condition deteriorated rapidly. During the performance of an intravenous pyelogram searching for a primary lesion, respiratory difficulties developed which required endotracheal intubation. This was followed by exploration of the posterior fossa. A large necrotic tumor was removed from the left cerebellar hemisphere. The patient did not improve and died nine days later. The surgical specimen on microscopic study showed the cerebellar folia to be replaced by neoplastic tissue. The leptomeninges were invaded with tumor cells having large eccentric nuclei and stellate cell processes. Vascular hyperplasia and necrosis abounded throughout the tumor (Fig. 4).

CASE 3. A white physician, age 39, complained of headache and diplopia of six months' duration. He had two brief episodes during which his gait was disturbed. Past history not relevant.

When admitted to the hospital he was quite comfortable except for diplopia. Bilateral papilledema and enlarged blind spots were noted. Brain scan and EEG were normal. Angiography demonstrated an avascular mass in the left cerebellar hemisphere (Fig. 5). Posterior fossa exploration disclosed a large greyish pink mass presenting on the surface of the left cerebellar hemisphere. The tumor was easily separated from the surrounding seemingly normal tissue. The postoperative recovery was uneventful. Radiation therapy was given. The patient remained well and without symptoms for more than a year, when recently he began to have headache, vomiting, and ataxia once more. Microscopic study showed replacement of cerebellar parenchyma by cellular pleomorphic tumor. Some neoplastic cells had large vesicular nuclei and stellate cytoplasmic processes. Giant cells and multinucleated cells were present throughout the tumor. Neoplastic cells invaded the leptomeninges with a secondary intense connective tissue reaction. Vascular hyperplasia and necrosis were found (Fig. 6).

Excluding schwannomas of the cerebello-pontine angle, most posterior fossa



FIG. 3. Case 2. Left brachial angiogram showing a left cerebellar mass.

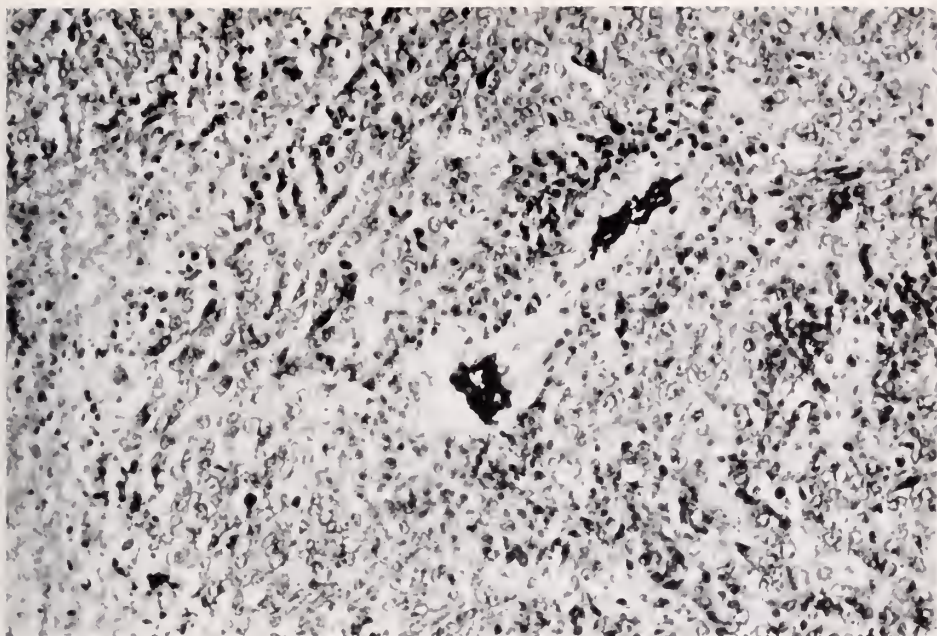


FIG. 4. Case 2. Photomicrograph showing necrosis and hyperplastic blood vessels bordered by aggregates of tumor cells.



FIG. 5. Case 3. Right brachial angiogram shows an avascular left cerebellar mass.

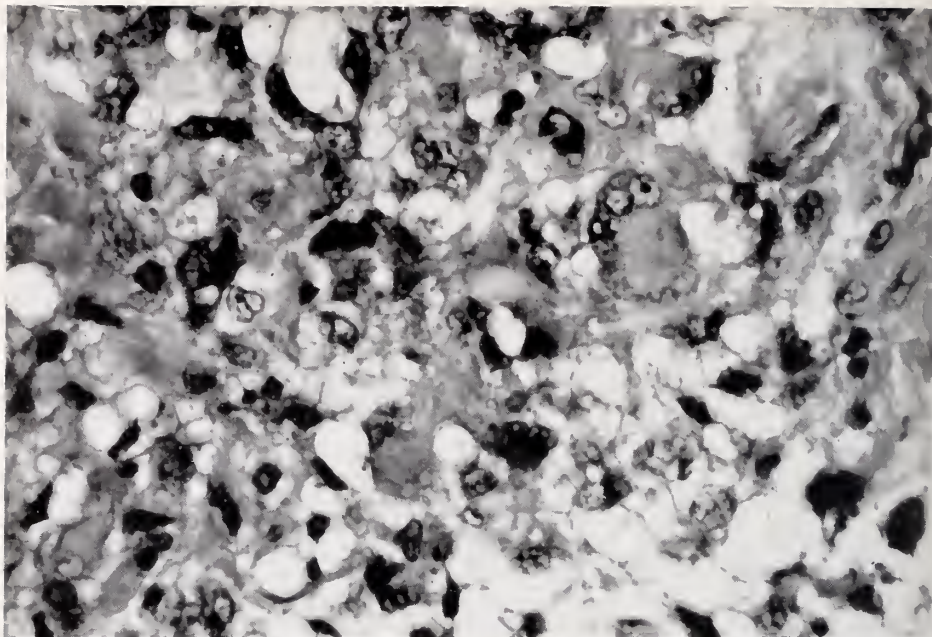


FIG. 6. Case 3. Photomicrograph showing pleomorphism, bizarre cells, and multinucleated giant cells.

tumors in adults fall into three groups: metastatic, hemangioblastomas, or meningiomas. The discovery of three cerebellar glioblastomas in adults within a matter of a few months can be nothing more than happenstance. The rarity of posterior fossa glioblastomas is confirmed by the paucity of reported cases in the literature.

Our first two patients were not observed until late in their course so the results of operative treatment can not be fairly judged. The third patient remained in relatively good condition for over a year. Surgical treatment and radiotherapy has resulted in an excellent temporary result with restoration to an almost normal state for more than a year when symptoms recurred. It is not possible from our limited experience to comment meaningfully on the biologic characteristics of glioblastomas of the cerebellum, however, most likely they behave much like supratentorial glioblastomas. Past experience with brain tumors has taught us that the microscopic appearance presents only one facet of perhaps many aspects in the life history of a neoplasm.

References

1. Bailey, P., and Cushing, H.: *Tumors of the Glioma Group*, J. B. Lippincott, Philadelphia 1926.
2. Bailey, P.: *Die Gewebsverschiedenheit der Hirngliome*, Fisher, Jena 1930.
3. Bailey, P.: *Intracranial Tumors*, C. C Thomas, Springfield 1933.
4. Bailey, P., Buchanan, D., and Bucy, P.: *Intracranial Tumors of Infancy and Childhood*, Univ of Chicago Press, Chicago 1939.
5. Cushing, H.: *Intracranial Tumors*, C. C Thomas, Springfield 1932.

6. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme, Arch Neurol and Psych 14:139, 1925.
7. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie. W. de Gruyter, Berlin 1922.
8. Stern, R. O.: Cerebral Tumors in Children. A Pathologic Report, Arch Dis Childhood, 12:291, 1937.

Received for publication October 1, 1968

CLINICO-PATHOLOGICAL CONFERENCE

Polycythemia and Transient Hypoglycemia in a 77-Year-Old Male

Edited by

FRANKLIN M. KLION, M.D.

A 77-year-old white man was transferred to The Mount Sinai Hospital for evaluation of hypoglycemia.

The patient had polycythemia vera for approximately ten years which was treated with phlebotomies and one course of P³². He received 10 units of blood five years prior to admission for bleeding following a suprapubic prostatectomy. He required nitroglycerin for occasional chest pain.

Three months prior to entry he was hospitalized for severe right sciatic pain following an injection of a mercurial diuretic for edema of the lower extremities. His hemoglobin was 7 gm%, hematocrit 28%, white cell count 78,000/mm³ with 83% polys, 9% band forms, 3% lymphocytes, 2% eosinophils, and 1% basophils. The platelet count was 894,000/mm³, and serum iron was 50 µg% with a total binding capacity of 608 µg%. Following two units of whole blood and oral iron therapy, the hemoglobin rose to 12 gm% and the hematocrit to 46%. A fasting blood sugar was 38 mg%, serum sodium 132 mEq/L, potassium 4 mEq/L, chlorides 95.7 mEq/L, and CO₂ 22.8 mEq/L. The SGOT was 34 units and the SGPT 38 units.

One month later he was readmitted to the hospital because of severe lower abdominal pain, headaches, anorexia, and dull chest pain. A disseminated guttate rash was present over the trunk and extremities, and a firm, nontender spleen was palpable four fingerbreadths below the left costal margin. The patient was begun on a 10 percent glucose infusion, following which the blood sugar rose to 177 mg%. When intravenous glucose infusions were discontinued, the blood sugar fell to 19 mg%, and he complained of a slight headache, malaise, and was slightly confused. He was placed on a high protein diet with frequent feedings, and his blood sugar was maintained at 140 mg%. However, if feedings were more than four hours apart, he became hypoglycemic. The 24-hour urinary ketosteroid excretion was 3.85 mg%, and 17-hydroxycorticosteroid excretion 3.07 mg%. An intravenous glucose tolerance test showed a fasting blood sugar of 11 mg%, one half-hour value of 92 mg%, one hour 97 mg%, two hours 103 mg%, and three hours 125 mg%. One half hour after intramuscular injection of 1 cc of glucagon the blood sugar rose from 66 to 115 mg%. The SGPT was 38 units and the acid phosphatase activity 5.5 King-Armstrong units. The serum albumin was 3.6 gm%, globulin 1.94 gm%, uric acid 9.9 gm%, total serum bilirubin 1.25 mg% with 0.5 mg% direct reacting. Stool examinations showed occasional occult blood. The total serum cholesterol was 147 mg%. Urinalysis revealed a trace of albumin and was otherwise unremarkable. The electrocardiogram was within normal limits.

An x-ray examination of the dorsal and lumbar spine showed degenerative changes at L 3-4 and L 4-5, as well as osteoarthritis of the lower dorsal and lumbar spine. X-ray examinations of the skull were normal. A skin biopsy was reported as parapsoriasis.

He remained asymptomatic except during periods of hypoglycemia which were promptly relieved by parenteral or oral administration of carbohydrates. On the tenth hospital day, he was transferred to The Mount Sinai Hospital for further evaluation.

He was a thin, undernourished elderly man who was slightly confused but in no acute distress. The blood pressure was 100/70, pulse 87/min and regular, respirations 20/min, and temperature 99.4°F. The lungs were hyperresonant and there were scattered inspiratory and expiratory rales at both bases. The point of maximum cardiac impulse was in the fifth intercostal space to the left of the midclavicular line. A Grade I late systolic murmur was heard along the left sternal border. The liver was palpated two fingerbreadths below the costal margin, and the spleen was hard and irregular and palpated three fingerbreadths below the left costal margin.

The hemoglobin was 13.8 gm%, hematocrit 56%, reticulocyte count 3.6%, platelets 600,000/mm³, and the white cell count was 97,000/mm³, with 24% band forms, 70% segmented forms, 4% eosinophils, 1% basophils, and 1% lymphocytes. The mean corpuscular volume was 85 μ^3 , mean corpuscular hemoglobin 20.5 gamma, and mean corpuscular concentration 34.5%. The peripheral blood smear showed anisocytosis, poikilocytosis, hypochromia, and an occasional giant platelet. A bone marrow was hypercellular with erythroid hyperplasia. Haptoglobins were 79 mg% and the fibrinogen was 255 mg%. The serum sodium was 143 mEq/L, potassium 4.0 mEq/L, chlorides 96 mEq/L, and CO₂ 14.5 mEq/L. The BUN was 37 mg% and the total protein was 6.5 mg, with 3.8 gm% albumin and 2.6 gm% globulin. The total serum cholesterol was 150 mg%, alkaline phosphatase activity was 18.6 King-Armstrong units, SGOT 23 units, SGPT 27 units, uric acid 8.0 mg%, and creatinine 1.1 mg%. The serum folate level was 16 $\mu\text{g}/\text{ml}$ and the B₁₂ level was 1841 $\mu\text{g}/\text{ml}$. A Coombs' test was negative, and a Wasserman test was slightly reactive. A serologic test for syphilis, performed on cerebrospinal fluid, was negative. Electrophoresis of the serum showed an albumin of 56.5%, alpha₁ 5.1%, alpha₂ 8.2%, beta 11.8%, and gamma globulin 18.4%.

A fasting blood sugar on admission was 82 mg%. An oral glucose tolerance test performed on the sixth hospital day revealed a fasting blood sugar of 130 mg%, one half hour 190 mg%, one hour 152 mg%, two hours 112 mg%, three hours 80 mg%, four hours 82 mg%, and five hours 78 mg%. The stool was positive for occult blood. A white cell count on the 18th hospital day was 112,000/mm³ with 9% band forms, 89% segmented forms, 1% eosinophils, and 4% lymphocytes. A culture of the urine grew greater than 300,000 colonies of *B. proteus*. An electroencephalogram revealed bilateral, diffuse cerebral dysfunction, most marked on the left. A sonencephalogram and a left carotid angiography performed on the 24th hospital day were normal. An electro-

cardiogram was normal. A repeat bone marrow aspiration showed 1% metamyelocytes, 13% bands, 29% segmented forms, 1% eosinophilic band forms, 16% lymphocytes, 4% reticulum cells, 2% proerythrocytes, 16% erythrocytes, and a myeloid-erythroid ratio of 4:1. The smear was very cellular with some areas packed with myeloid precursors.

The patient displayed increasing agitation and confusion, and complained of chest pain. In addition, he noted a feeling of suffocation. Examination revealed no significant abnormalities.

Streptomycin and tetracycline were begun for the urinary tract infection, and the patient improved. A one-unit plasmapheresis was performed on the 25th day. Three weeks later his hemoglobin was 12.3 gm%, hematocrit 48%, reticulocyte count 2.7%, platelet count 202,000/mm³. The white cell count was 70,000/mm³ with 6% band forms, 88% segmented leukocytes, 2% eosinophils, 1% basophils, and 3% lymphocytes. The serum iron was 22 µg/100 ml, and total iron binding capacity 380 µg/100 ml. The fasting blood sugar was 70 mg%, BUN 31 mg%, and serum creatinine 1.4 mg%.

An x-ray of the upper gastrointestinal tract showed a small hiatal hernia, and a deformed duodenal bulb with no evidence of an ulcer crater. Occasional episodes of premature ventricular contractions were treated with dilantin. In addition, he received Maalox[®], tincture of belladonna, Thorazine and iron therapy. On the 54th hospital day, the patient's right wrist was noted to be slightly swollen and crepitant. An x-ray showed an osteolytic lesion. His temperature, which had been consistently below 100°F rose to 102°F. Chloromycetin[®] and hydrocortisone therapy was added. On the 56th hospital day, the BUN was 58 mg%, hemoglobin 12.3 gm%, and white cell count 114,000/mm³. The SGOT was 17 units and the SGPT 16 units. The patient became obtunded and expired two days later.

*Dr. Richard Bader**: When this man was admitted to another hospital for sciatic pain he was anemic and had typical laboratory finding of iron deficiency anemia. He was given whole blood and iron therapy, and his anemia improved. Furthermore, he had some form of myeloproliferative disorder or leukemia suggested by the very high white blood cell count. The serum electrolytes were normal but the blood sugar was 38 mg%. However, patients who have very high white counts may have low blood sugars if the blood is left in the test tube for several hours before the determination is made. This occurs even in fluorinated specimens because of the consumption of the sugar by the large number of white blood cells. Typically, the blood sugar may fall to 50 mg% in two to three hours, so that a blood sugar of 38 mg% is low, even if we consider artefactual hypoglycemia. However, so-called artefactual hypoglycemia does not cause symptoms. This patient had true hypoglycemia.

He had been treated for polycythemia vera, and following a prostatectomy he had severe bleeding. Hemorrhage during operations in patients with polycythemia is a well known complication. The exact cause of hemorrhage in these

* Associate Clinical Professor, Department of Medicine, Mount Sinai School of Medicine, New York.

patients is not well understood, but may be related to the increased number of platelets which have impaired function. Control of the polycythemic state reduces the tendency to bleeding, and bleeding is less likely the longer the duration of control. In any case, the patient had polycythemia vera but still manifested a leukenoid blood picture.

His 24 hour urinary ketosteroid excretion was low but he was a very thin person and the excretion of 17 ketosteroids is related to body mass. Since there was no evidence of electrolyte abnormality or other stigmata suggestive of adrenal insufficiency, I am not inclined to make a diagnosis of adrenal or pituitary insufficiency.

An intravenous glucose tolerance test done at another institution showed a very low fasting blood sugar which rose to 125 mg% after three hours. A carbohydrate diet for several days prior to the test might have accentuated a hypoglycemic response if he had true hypoglycemia, since hypoglycemia may occur after the initial rise in the blood sugar. A six hour glucose tolerance test is more helpful.

Following an injection of glucagon, the blood sugar rose from 55 mg% to 115 mg% in half an hour. In normal individuals the blood sugar rises in 30 minutes. In patients with hypoglycemia, the blood sugar should fall to hypoglycemic levels within 90 to 180 minutes. When the glucagon test is used to investigate hypoglycemic syndromes, the test must be carried out for 180 minutes. The tolbutamide test is another method for evaluating hypoglycemia. One gram of tolbutamide is injected intravenously over a period of two minutes and blood sugars are observed for a period of three hours. In functional hypoglycemia, the blood sugar should return to 70 percent of fasting levels by three hours. In patients with true insulin-producing tumors, it does not. The tolbutamide and glucagon tests are used also in combination with insulin assays, to give more refined information in the presence of insulin-secreting tumors.

In this particular patient, neither the glucagon test nor the glucose tolerance test were helpful in the differential diagnosis, since longer periods of observation of the blood sugar values were necessary. The patient was asymptomatic except for the hypoglycemic episodes which were promptly relieved by parenteral or oral carbohydrates. Whipple's triad of early morning hypoglycemia used to be considered diagnostic of insulinoma, but it is not, since other conditions can mimic an islet cell tumor.

The serum acid phosphatase activity was elevated. I shall assume if he had benign prostatic hypertrophy, residual prostatic tissue or possibly an early carcinoma of the prostate could account for this slightly elevated activity. However, thrombocytosis may also cause an elevation of acid phosphatase activity.

The white cell count was also elevated with a shift to the left, and the low mean corpuscular hemoglobin concentration, low hematocrit and hemoglobin would be expected in iron deficiency.

The bone marrow was hypercellular with erythroid hyperplasia, and the

serum B₁₂ level was markedly elevated. Although these findings are compatible with a myeloproliferative disorder, hepatic tumors are also capable of producing polycythemia and hypoglycemia. While hepatic replacement can cause hypoglycemia, it does not cause polycythemia. Therefore, I do not think we are dealing with a tumor-producing secondary polycythemia. In addition, it would not have been present for ten years. The B₁₂ level is elevated in myeloproliferative disorder as well as in myelocytic leukemia. Whereas in myelocytic leukemia there is a normal or low white cell alkaline phosphatase, there is an increased or normal alkaline phosphatase in the myeloproliferative disorders. However, rather than use the term "myelogenous leukemia," the term "leukemoid reaction" in the spent phase of polycythemia or myeloid metaplasia would probably be more desirable. It is not always associated with a shift in the white cell count, reduced alkaline phosphatase activity, or the presence of abnormal chromosomes of the Philadelphia type.

I was amazed that the carbon dioxide content was 14.5 mEq/L. He was not tachypneic so that a respiratory alkalosis would be unlikely. Possibly the metabolic acidosis was a reflection of mild starvation.

The glucose tolerance test performed at this hospital revealed mild glucose intolerance. A diabetic type of tolerance curve may be seen in patients with functional hypoglycemia, and also in normal patients when carbohydrate intake has been limited. During his final admission he no longer experienced hypoglycemic episodes, and improved markedly when streptomycin and tetracycline were begun for a urinary tract infection. Possibly this was coincident with treatment of a mild hypostatic pneumonia.

An x-ray of the upper gastrointestinal tract showed a small hiatus hernia and a deformed duodenal bulb, with no evidence of an ulcer crater. Since duodenal ulcers are a common finding in polycythemia vera, he was treated with anticholinergic and antacid therapy.

On the 54th hospital day, the patient's right wrist became swollen and an x-ray showed an osteolytic lesion. The radiolucent areas of the radius and ulna are consistent with either an enlarged marrow of the myeloproliferative disorder or possibly an osteolytic metastasis. Neither infection by a gas-forming organism nor trauma fracture appeared to explain the crepitation.

I think there is little question that he had a spent phase of polycythemia vera with myeloid metaplasia, characterized by a leukemoid blood count, a well-preserved red cell count, giant platelets, a high vitamin B₁₂ level, and hepatosplenomegaly. I assume he died as a result of two underlying diseases: myeloid metaplasia and a tumor, in addition to renal and pulmonary sepsis.

What was the cause of this man's hypoglycemia? He could have had an islet cell tumor of the pancreas, an extrapancreatic functioning tumor producing a hypoglycemic substance, a disease causing adrenal or pituitary insufficiency, or severe hepatic insufficiency with hypoglycemia. Other causes of hypoglycemia such as galactosemias, hereditary fructose intolerance may be eliminated because of patient's age and lack of associated abnormalities. Factitious hypoglycemia, that is, hypoglycemia induced by self-administration

of hypoglycemic agents, is also unlikely. There was no evidence of adrenal or pituitary insufficiency, with the exception of a low 17 ketosteroid determination. The angiogram, x-ray of the skull, and visual testing were normal.

The enlarged liver and a slightly elevated serum bilirubin is not unusual in patients with myeloid metaplasia and extramedullary hematopoiesis. Therefore, hepatic damage would be an unlikely cause of the hypoglycemia. The main problem to be considered is whether he had an islet cell tumor or a non-pancreatic tumor. In the past few years a variety of tumors have been described as capable of producing hypoglycemia. They have been mesothelial, epithelial, and endothelial in origin, and have been intraperitoneal, retroperitoneal, and thoracic in location. The large majority are fibrosarcomas. Whatever their pathology, they have usually been large and slow growing. Besides fibrosarcoma, a large number of hepatic carcinomas, adrenal cortical carcinomas, gastrointestinal carcinomas, bronchogenic carcinomas, and pseudomyxoma peritonei have been associated with hypoglycemia. The exact mechanism by which these tumors produce hypoglycemia is controversial. Six theories have been proposed. Over-utilization of glucose by the tumor cannot account for hypoglycemia based on quantitative estimations. Release of insulin, an insulin-like substance, an insulin potentiator, a beta cytotrophic stimulator, or a suppressor of counter-regulatory hormones from the tumor have all been considered. There is no evidence of release of insulin or an insulin stimulator from the tumor, and insulin assay in some of these cases has failed to demonstrate insulin. However, some investigators have demonstrated a polypeptide extracted from the tumors with hypoglycemic properties. The variability of the hypoglycemia suggests the tumor did not have a uniform output of a hypoglycemic substance, and leads me to believe it was an extra-pancreatic tumor, most likely a fibrosarcoma, producing a hypoglycemic substance.

In summary, my final diagnoses are:

1. Spent polycythemia vera with myeloid metaplasia and a leukemoid reaction.
2. Hypoglycemia due to a retroperitoneal tumor producing a hypoglycemic substance, most likely extrapancreatic.
3. Terminal sepsis, urinary and pulmonary.

*Dr. Stephen A. Geller**: The pathologic discussion may be divided into incidental findings, abnormalities of the hematopoietic system, and the etiology of hypoglycemia. One of the incidental findings consisted of fibroadenomatous hyperplasia of a small portion of the remaining prostate gland, and probably explains the elevated alkaline phosphatase activity.

The kidneys were slightly reduced in size and showed mild arterial and arteriolar nephrosclerosis.

Both lungs were increased in weight due to edema, and marked congestion, and some of the congested vessels showed early thrombus formation (Fig. 1).

* Chief Resident, Department of Pathology, The Mount Sinai Hospital, New York.

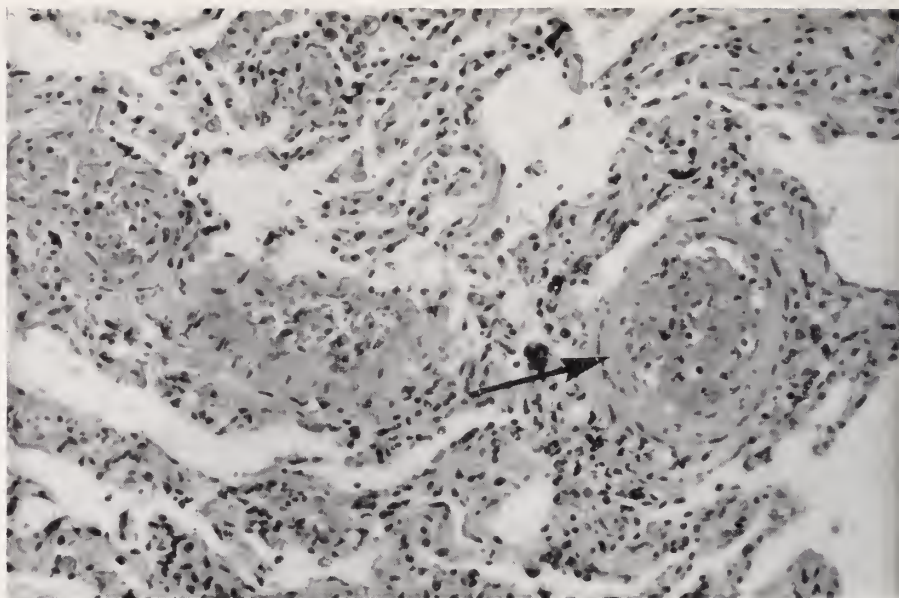


FIG. 1. Photomicrograph of organizing thrombus (arrow) in small pulmonary artery (hematoxylin and eosin, $\times 100$).

In addition, there was a small cylindrical pedunculated angiomyoma on the posterior aspect of the right upper lobe.

There were many colonic diverticula, and the colon contained a small amount of black fecal material. One centimeter distal to the pyloric ring there was a deep, irregular ulcer crater, but there was no evidence of recent bleeding (Fig. 2). The ulcer was probably one manifestation of polycythemia vera, as was the enlarged spleen which weighed 1,520 grams. The capsule was irregularly depressed by multiple areas of infarction. However, adjacent to the infarcted areas, the parenchyma was well preserved (Fig. 3). Although congested by erythroid and myeloid precursors, occasional atypical blast forms and giant multinucleated megakaryocytes were seen.

The liver weighed 2,100 grams and also showed a focal zone of infarction. The architecture was normal but a mild diffuse, myelogenous infiltrate was seen throughout the sinusoids and in the portal tracts. Scattered areas of centrilobular necrosis were probably related to the terminal hypotension. In addition, the portal vein showed a small nonoccluding adherent thrombus. The abdominal lymph nodes were small, but the sinusoids were filled with many myelogenous cells.

The vertebral marrow showed an increase in reticulum fibers and many myelogenous and erythroid precursors and megakaryocytes (Fig. 4). Myelogenous leukemia was considered clinically, but can be ruled out anatomically by the size of, and the pleomorphism of the cells in, the liver and the lymph nodes. Although the Philadelphia chromosome has not been demonstrated in myeloid metaplasia, chromosome abnormalities have been reported in as many



FIG. 2. Stomach and duodenum showing large, irregular ulcer crater (arrow) in postpyloric region.

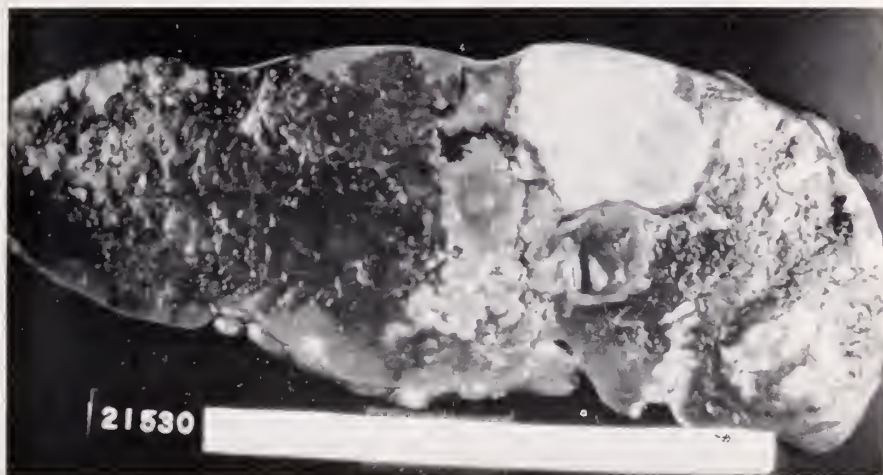


FIG. 3. Cut section of spleen showing congestion and large, irregular zones of infarction.

as 52 percent of cells cultured from patients having myeloid metaplasia. Myeloid metaplasia was described in 1879 by Hueck in *Virchows Archiv für Pathologische Anatomie und Physiologie und für Klinische Medizin*. In the intervening 90 years, little has been added to our understanding of the mechanism of this disease. The proliferative diseases which include polycythemia vera, must be thought of as a continuum of a single precursor cell in which

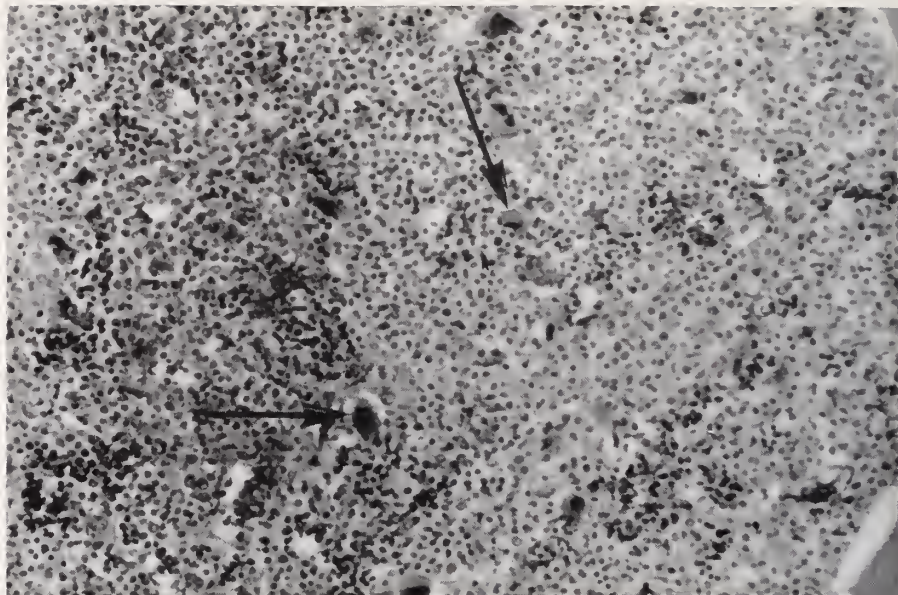


FIG. 4. Photomicrograph of bone marrow showing many megakaryocytes (arrows), and cells of the myeloid series (hematoxylin and eosin, $\times 100$).

components proliferate at various speeds and various intensities, so that it is sometimes difficult to separate leukemia from myeloid metaplasia. It was suggested that polycythemia vera was due to a narrowing of the blood vessels of the bone marrow, with anoxemia and compensatory polycythemia. This mechanistic explanation has never been verified, and the etiology is still not clear. It may be that a defect in feedback exists from one of these intermediate precursors, permitting an exponential flow of cells into one of the compartments. There is some recent evidence that the defect resides in the primitive cell itself. Myeloid metaplasia has been said to complicate polycythemia vera in as many as 20 to 25 percent of patients. The most frequent complication of polycythemia vera, however, is thrombosis.

The heart was slightly enlarged. The left ventricular wall appeared thin, but the papillary muscles showed evidence of true hypertrophy, obscured by the dilatation of ventricle and atrium. Under the mitral valve and infiltrating into the musculature was an organizing thrombus (Fig. 5). A similar thrombus was found in the right atrium. The coronary arteries were not significantly narrowed, but they showed mild atherosclerosis. Some of the vessels, deep in the myocardium, also showed thrombosis, which led to scattered areas of myocardial ischemia with subsequent fibrosis, and may have been responsible for the chest pain which was clinically unexplained (Fig. 6).

Finally, what caused the hypoglycemia?

The pancreas was normal. However, the left kidney was surrounded by a large, lobulated, partially cystic tumor mass which did not invade the renal

parenchyma, but was indistinguishable from the capsule (Fig. 7). The major portion of the tumor was soft and yellow, and specifically stained for fat. Scattered throughout the tumor were many large hyperchromic lipoblasts, characteristic of a low grade retroperitoneal liposarcoma (Fig. 8). Tumors of fat-forming cells, both benign and malignant, are among the least studied and most fascinating aspects of oncology. Lipomas are almost endemic and yet malignant fat tumors are rare, and evidence of their malignant potential is often lacking because they metastasize late. These tumors may be enormous in size. The largest tumor was recorded by Dalamater in 1859, weighing 275 pounds.

There have been three extensive reviews of hypoglycemia in association with an extrapancreatic neoplasm. Although Elliot and Nadler described the first case of hypoglycemia associated with a tumor, Doege, a surgeon, and Potter, a radiologist, are credited for the syndrome. They described a fibrosarcoma weighing approximately 2,400 grams removed by open thoracotomy under



Fig. 5. Heart, showing large organizing thrombus beneath mitral valve, appearing to infiltrate adjacent myocardium (arrows).

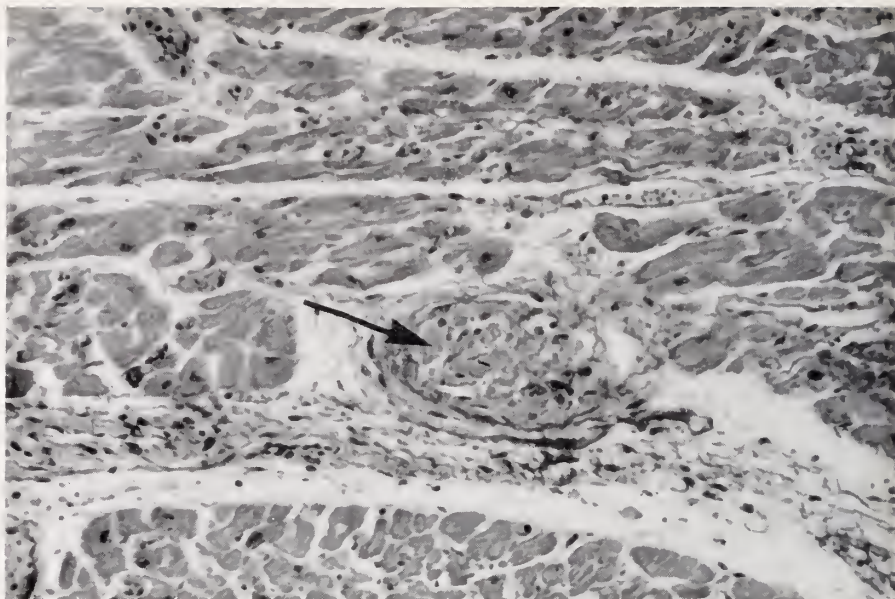


FIG. 6. Photomicrograph of thrombosed coronary vessel (arrow) deep in myocardium (chromotrope aniline blue, $\times 100$).

local anesthesia. The patient had maniacal symptoms ascribed to interference with venous return from the brain by the tumor, which was located near the superior vena cava. It was not until seven years later that they related the symptoms to a low blood sugar which could be relieved by intrarectal glucose infusion. The patient died in 1934, seven years after thoracotomy because of intestinal obstruction from bilateral strangulated inguinal hernias. Other humoral syndromes, including amenorrhea, masculinization, gynecomastia as well as atrophy of the breasts, have been described in association with tumors, particularly adrenal carcinoma. In addition to the cases reported in these reviews, at least 27 other cases have been described.

In 1962, Tranquada reported the first case of hypoglycemia associated with a true epithelial tumor. This patient had a testicular feminizing syndrome with a Leydig cell adenoma of his testicle-ovary. Bioassay of this tumor demonstrated high insulin activity. Some hepatomas are also associated with polycythemia and hypercalcemia, but perhaps hepatomas should be distinguished from other tumors because hypoglycemia may be due to hepatic insufficiency. Increased plasma erythropoietin has not been consistently demonstrated, and the hypercalcemia has been ascribed to production of a parathormone-like substance. Neuroblastoma and Wilms' tumors, in infants and children, have been associated with hypoglycemia.

The present case represents the second liposarcoma described in association with hypoglycemia, and the first associated with polycythemia vera. As Dr. Bader mentioned, several mechanisms of hypoglycemia have been postulated (Fig. 9). One interesting theory suggests that insulin in the fasting state

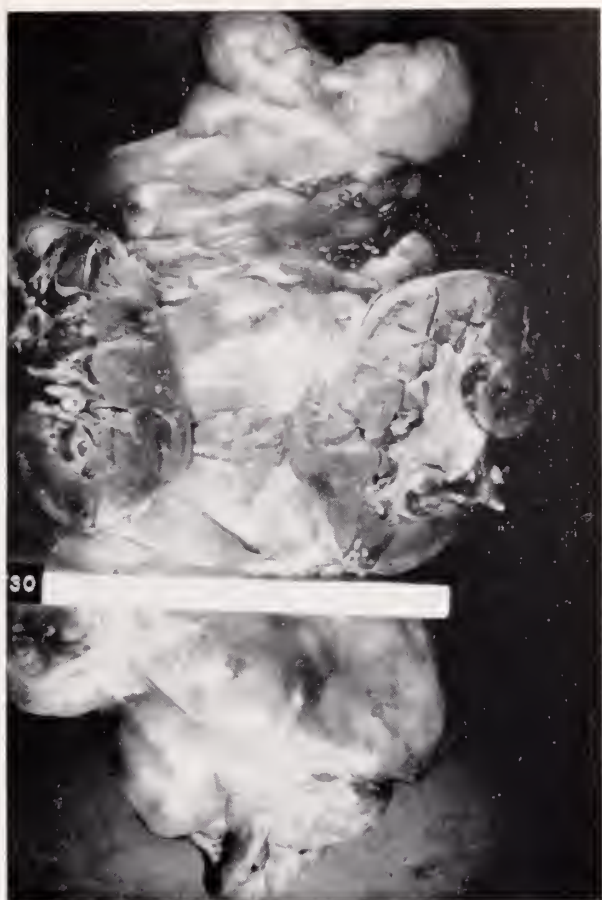


Fig. 7. Large perirenal liposarcoma surrounding left kidney which has been bisected.

circulates as a complex with a protein. This binding is most likely catalyzed in the liver. The insulin complex may be dissociated by fibroareolar tissue and other factors, and the "free" insulin then exerts its metabolic effect. It is postulated that the sarcoma acts as the dissociating factor, but implies an increased insulin production by the pancreas, which has not been demonstrated. Decrease of hepatic glucose production has been demonstrated in some cases. However, many cases have shown normal and even high glucose production by the liver. Massive infiltration of the liver may explain hypoglycemia associated with hepatomas, but many cases show little or no liver infiltration. An absence of glucose-6-phosphatase was demonstrated in one hepatoma, but was not substantiated in subsequent studies.

There are many reports of insulin-like activity by bioassay methods. Insulin-like activity has also been demonstrated *in vitro* by the ability of tumor tissue to form glycogen from C_{14} labeled glucose, an action considered to be a specific activity of insulin which can be blocked by insulin antibodies and

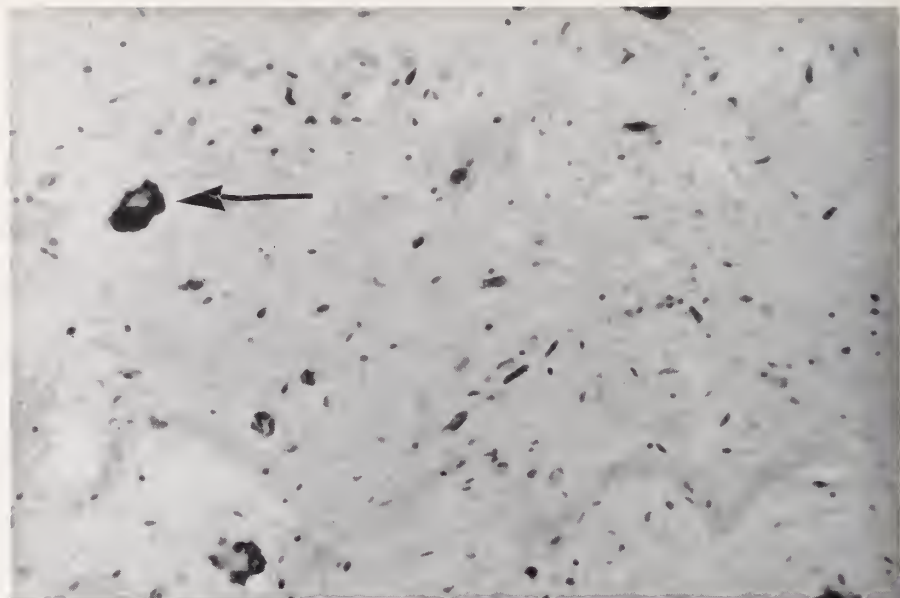


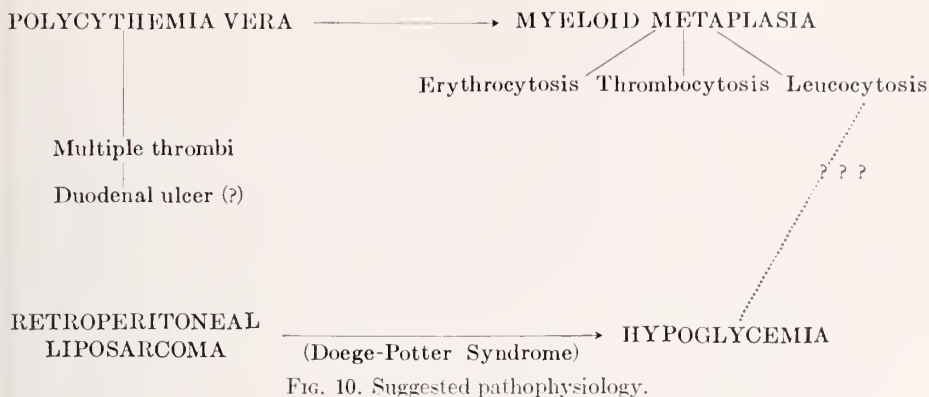
FIG. 8. Photomicrograph of liposarcoma showing giant lipoblasts (arrows) (hematoxylin and eosin, $\times 100$).

sulfhydryl inhibitors. No hypoglycemic tumor has ever been found to contain immunoassayable insulin. Immunoassayable insulin and glucagon were found in a case of metastatic bronchogenic carcinoma, and were attributed to a "sponging" mechanism, but the patient was not hypoglycemic.

Dr. Berson reported seven patients in whom he was unable to demonstrate hyperinsulinism in plasma, or significant insulin concentration in tumor extracts. The unusual glucose tolerance curves seen in these patients are frequently of the diabetic type and can be explained by a hypothetical feedback mechanism. The tumor utilizes large quantities of glucose so that beta cell activity becomes depressed in an attempt to compensate for the systemic glucose deprivation. When a test dose of glucose is given, the tumor is temporarily satisfied, and there is a lag in insulin release. I feel the large

1. Interference with the cerebral circulation.
2. Mechanical action of the tumor on the splanchnic nerve and ganglion.
3. Glucose hunger.
4. Adrenocortical insufficiency.
5. Activity of ectopic islet cell tissue.
6. Pressure on autonomic neuroreceptors of the liver.
7. Secretion of insulinase inhibitor.
8. Production of insulin-like substance, or insulin potentiator.
9. Inhibition of hepatic insulinase.
10. Production of beta cytotropic substance.
11. Deficient hepatic glucose production.
12. Dissociation of the normally protein-bound insulin by the tumor.
13. Release of stored insulin from tumor ("sponging").
14. Production of glucose-metabolism-interfering-factor.
15. Factitious.

FIG. 9. Suggested mechanisms of neoplasia-induced hypoglycemia.



size of these tumors is of major importance. However, the possibility of a secreted insulinoïd factor cannot be eliminated.

In summary (Fig. 10), the patient had a liposarcoma associated with hypoglycemia. Myeloid metaplasia was probably coincidental, but *in vitro* digestion of glucose, by leukocytes, may have contributed to the extremely low glucose levels.

*Dr. Solomon Berson**: In the early 1960's, we reported two cases of extra-pancreatic tumors in which the plasma insulin activity was elevated. One of these was a neuroepithelioma with widespread metastases. The other was a gastric carcinoma. A few years later, the patient with the neuroepithelioma died and at post mortem he had an islet cell adenoma of the pancreas. Therefore, a thorough search for an islet cell adenoma of the pancreas must be performed in all patients with hypoglycemia.

In the second case, there were extensive metastases to the pancreas. We could not extract a hypoglycemic factor from the carcinoma itself, so we considered the possibility of secondary stimulation of the islet cells.

So far as the glucose tolerance test is concerned, one may have a diabetic curve even in the presence of an islet cell adenoma, and I think your explanation probably is as good as any. The glucagon test is performed to evaluate the ability to mobilize glucose. The insulin secreting activity of glucagon was first discovered because glucagon produces an early fall in blood sugar rather than a rise in patients with functioning islet cell adenoma. It followed that pancreatic glucagon and probably also gut glucagon, are true stimulators of insulin release. I agree that factitious induced hypoglycemia may lack pathologic findings, but I would have you recall a very famous murder case in England which was solved by an insulin assay performed at the site of injection.

Speaker from the Floor: Is hypoglycemia associated with the pancreatic adenoma less likely to be intermittent than from retroperitoneal tumors?

Dr. Berson: Both may be labile. I would have thought a tumor would more

* Professor and Chairman, Department of Medicine, Mount Sinai School of Medicine, New York.

likely have produced constant hypoglycemia. That the patient did have a spontaneous remission is rather interesting.

Dr. Geller: A few of the cases reported showed a fluctuating course. After a few months of remission, hypoglycemia recurred.

Speaker from the Floor: How useful is the leucine infusion test?

Dr. Berson: Leucine is perhaps more valuable than the tolbutamide test.—The ordinary dose of leucine produces only a slight fall in blood sugar in normal patients. However, it will not differentiate an islet cell adenoma from idiopathic hypoglycemia.

Final Diagnosis:

(POLYCYTHEMIA VERA).

MYELOID METAPLASIA.

RETROPERITONEAL LIPOSARCOMA, PRODUCING HYPOGLYCEMIA.

MURAL THROMBUS, LEFT VENTRICLE.

MURAL THROMBUS, RIGHT ATRIUM.

PORTAL VEIN THROMBOSIS, NONOCCLUSIVE.

ARTERIOLE AND CAPILLARY THROMBOSES OF MYOCARDIUM.

MYOCARDIAL NECROSIS, FOCAL.

ANGIOMYOMA, RIGHT LOWER LOBE OF LUNG.

CHRONIC DUODENAL ULCER.

HEPATOMEGALY.

SPLENOMEGALY, WITH MULTIPLE INFARCTS.

References

- Frantz, V. K.: *Tumors of the Pancreas*. Armed Forces Institute of Pathology Atlas of Tumor Pathology, Fascicle H 28-29, 1959.
- Ginsberg, D. M.: Hypoglycemia Associated with Extrapaneareatic Neoplasms, *Advances Intern Med*, 12:33, 1964.
- Lowber, L.: Hypoglycemia Producing Extrapaneareatic Neoplasms. *Amer J Clin Path* 35:233, 1961.
- Papaioannou, A. N., and McPeak, C. J.: Rhabdomyosarcoma of the Buttock Producing Hypoglycemia, *Ann Surg* 161:553, 1965.
- Tranquada, R. E., Bender, A. B., and Biegelman, P. M.: Hypoglycemia Associated with Carcinoma of the Cecum and Syndrome of Testicular Feminization, *New Eng J Med* 266:1302, 1962.
- Unger, R. H.: The Riddle of Tumor Hypoglycemia, *Amer J Med* 40:325, 1966.
- Yalow, R. S., and Berson, S. A.: Dynamics of Insulin Secretion in Hypoglycemia, *Diabetes* 14:341, 1965.

Received for publication November 18, 1968

RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., Co-EDITORS

CASE NO. 313

A 26-year-old man was inadvertently struck on the anterior aspect of the neck by the elbow of a fellow player in a softball game in a karate-like action. He immediately experienced difficulty in breathing and talking and was brought to the hospital emergency room. Direct laryngoscopy revealed edema and diminished mobility of the vocal cords. The patient was admitted to the hospital and observed closely with the possibility of tracheotomy in mind. His condition stabilized and improved progressively with medical therapy which included steroids, antihistamines and steam inhalations.

Radiographic study of the soft tissues of the neck was performed shortly after admission. In the frontal projection, the tracheal air column was displaced to the left of the midline and its right margin was encroached upon by soft tissue shadow (Fig. 1). Tomography was performed on the day after admission. The soft tissues on the right side of the larynx were abnormally prominent and the pyriform fossa and the ventricle were totally obscured. The left true and false cords were thickened and the subglottic space was asymmetric (Figs. 2 and 3).

Direct laryngoscopy was again performed 4 days later. Hematoma was seen in the right pyriform fossa with edema of the right side of the larynx, and these clinical findings accounted for the radiographic appearance. The patient was discharged 2 days later.

Tomography was repeated one month later, at which time the patient was asymptomatic. The larynx was normal except for slight asymmetry of the pyriform fossae (Fig. 4).

Discussion

Laryngeal trauma is life endangering because it may compromise the airway. While the clinical picture may appear to be stable, symptoms may suddenly progress with dramatic speed, since slight diminution in the diameter of the airway may tip the scales away from respiratory compensation. Provision for tracheotomy must therefore be on hand and the patient observed closely at all times.

Hematoma and edema produce classical roentgen changes in the soft tissues, with deformity and encroachment on the surrounding and contrasting air column. Not only can one compare the asymmetry of the pyriform fossae, ventricles, cords and subglottic region during the acute phase, but restoration of these structures to normal after an interval is of further illustrative value. While positive contrast laryngography is a very useful and elegant procedure, it was contraindicated in this case because of the risk of further compromise of the airway, in the absence of a tracheotomy in situ. In a different age



Case 318, Fig. 1. Anteroposterior radiograph of the neck reveals the tracheal air column displaced to the left of the midline. Arrows point to the right margin of the column which is encroached upon by soft-tissue shadow. The left margin is smooth.



Case 318, Fig. 2. Frontal tomogram at the 17 cm level made during phonation reveals full soft-tissue shadow all along the right margin of the larynx. The pyriform fossa and the ventricle are totally obscured and the subglottic space is asymmetric. On the left side, the true and false cords are both thickened.



Case 318, Fig. 3. Frontal tomogram at the 17 cm level made during quiet respiration reveals full, slightly lobulated soft-tissue shadow on the right side of the larynx as the cords relax bilaterally. The right pyriform fossa is totally obscured.



Case 318, Fig. 4. One month later, frontal tomogram at the level comparable to Figs. 2 and 3 made during phonation now reveals only slight asymmetry of the pyriform fossae with the right side less air-containing than the left. The true and false cords, ventricle, and subglottic region are normal and symmetrical.

group or a different set of clinical circumstances, neoplasm or even chronic granulomatous disease might also produce similar roentgen features, but these are of no consideration in this case.

Case Report: HEMATOMA OF THE LARYNX.

Acknowledgment

This case is presented through the courtesy of Dr. Akbar Nossoughi, Good Samaritan Hospital, Suffern, N. Y.

CASE NO. 319

A 31-year-old male was seen by his physician following a twisting injury to his right knee. Past history revealed that deformities of both his elbows had been noted at age 10 and that his mother had a similar appearance to her elbows. Radiographs had not been obtained.

On examination the patient was of very short stature (approximately 5'3"). The nails of all digits of hands and feet were hypoplastic and exhibited prominent longitudinal ridging. Both elbows were limited in extension and showed prominence laterally over the radial heads. The right knee was swollen and painful on motion. Both patellae were small and laterally placed. Symmetrical bony protuberances were palpable high on the posterior aspects of the iliac bones through the gluteal muscles.

Radiographic skeletal survey revealed the classical findings of Hereditary onycho-osteodysplasia. Symmetrical iliac bony protuberances—"iliac horns"—were seen in the pelvis along with moderate bilateral coxa valga (Fig. 1). Severe degenerative change and fragmentation was seen about the right lateral femoral condyle and both patellae were hypoplastic and laterally placed (Figs. 2, 3, and 4). The radial heads were deformed and subluxated



Case 319, Fig. 1. Anteroposterior radiograph of the pelvis and hips demonstrates symmetrical bony protuberances of the iliac bones termed "iliac horns" (arrows). These are posteriorly directed. Moderate bilateral coxa valga is also seen.



Case 319, Fig. 2. Anteroposterior radiograph of the right knee reveals extensive sclerosis and degenerative response in relation to the lateral femoral condyle. A small and fragmented patella overlies this region. A number of loose bodies are seen.

laterally and degenerative change with fragmentation was seen along the articular surfaces of the right elbow (Fig. 5).

The patient underwent surgery to the right knee. Patellectomy was performed, the osteochondritic areas of the lateral femoral condyle were debrided, and numerous loose bodies were extracted. The pathologist reported degen-



Case 319, Fig. 3. Tunnel projection of the right knee reveals the degenerative change and fragmentation to better advantage.

erated osteocartilagenous material and debris. The patient had good function and a normal range of motion 6 weeks later.

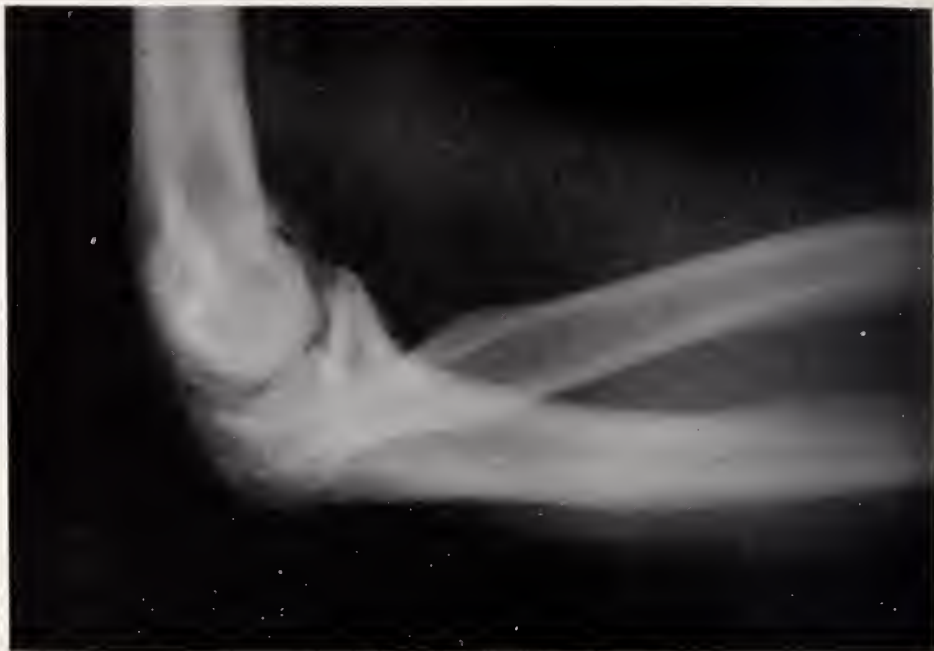
Discussion

Hereditary onycho-osteodysplasia is a well-documented syndrome of clinical findings, often referred to as "nail-patella" syndrome or "iliac horn" syndrome. References to this disease go back to the past century and many detailed studies are to be found in the recent literature (1). Extensive studies



Case 319, Fig. 4. Anteroposterior radiograph of the left knee reveals a hypoplastic, laterally placed patella (arrows) as well as a number of fragmented loose bodies.

on the hereditary pattern of transmission of the disease have indicated a non-sexlinked dominant inheritance pattern with a single gene locus closely related to that of the ABO blood groups (2). The radiographic features in the case presented are classical. In the pelvis, the characteristic finding is that of posterior bony projections from the iliac bones. In the English literature, these were first described by Fong and termed "iliac horns" (3). Coxa valga deformity is also common. In the knee, patellar abnormality ranges from hypoplasia to complete absence. The hypoplastic patella varies considerably in shape; it is often laterally placed, subluxated or completely dislocated, and



Case 319, Fig. 5. Lateral radiograph of the right elbow reveals marked degenerative change with fragmentation along the articular surfaces. The anteroposterior projection (not shown) revealed a deformed radial head subluxated laterally.

recurrent dislocations may be a serious disability. The lateral femoral condyle is also usually hypoplastic and the picture of severe osteochondritis dessicans, aseptic necrosis and fragmentation represents a far-advanced change. In the elbow, the carrying angle is increased due to a general hypoplasia of the lateral structures including the capitulum, the lateral epicondyle, and the radial head. The radial head may be enlarged and mushroomed and its articulation varies from lateral subluxation to complete dislocation. Severe degenerative changes may be present, often unilaterally.

Clinically, the dystrophic nails are usually very small with numerous longitudinal cracks and ridges, but a spectrum of variations in the extent and distribution of these dystrophic changes have been described. Skeletal anomalies of the fingers are not consistently present. A long list of additional defects have also been associated in various cases, but none of these by themselves are characteristic.

Case Report: HEREDITARY ONYCHO-OSTEODYSPLASIA.

Acknowledgment

This case is presented through the courtesy of Dr. Joel Adler, Good Samaritan Hospital, Suffern, New York.

References

1. Duncan, J. G., and Souter W. A.: Hereditary Onycho-Osteodysplasia, The Nail-Patella Syndrome, *J Bone and Joint Surg* 45B:242-258, 1963.
2. Duthie, R. G., and Hecht, F.: The Inheritance and Development of the Nail-Patella Syndrome, *J Bone and Joint Surg* 45B:259-267, 1963.
3. Fong, E. E.: "Iliac Horns" (Symmetrical Bilateral Central Posterior Iliac Processes). Case Report. *Radiology*, 47:517-518, 1946.

CASE NO. 320

A 17-year-old primagravida went into labor spontaneously at 37 weeks. Pregnancy had been uncomplicated except for severe asthma requiring drug therapy. General physical examination had revealed increased lumbar lordosis



Case 320, Fig. 1. Standing lateral projection from pelvimetry examination reveals the fetus in vertex presentation with occiput anterior, and the fetal spine almost horizontal with a protuberant abdominal wall. (Poor photographic reproduction.) The vertex is impinging on the sacrum below the promontory and shows evidence of molding.

and slight scoliotic curve to the left. The abdomen was quite protuberant and the uterus and fetus tended toward a horizontal orientation when the patient stood erect.

Despite good contractions, the fetal head remained high and progress was poor. Pelvimetry was requested. The films revealed a moderate scoliosis convex left and increased lordosis. The placenta was high on the posterior wall. The fetus was in vertex presentation with occiput anterior in the standing lateral projection. The abdominal wall was markedly protuberant and the fetus and uterus were almost horizontal (Fig. 1). The vertex of the fetal skull was impinging on the sacrum below the promontory as it engaged and showed evidence of molding. The anteroposterior inlet diameter measured 9.2 cm and the transverse inlet diameter measured 11.7 cm.

Although abnormal bony pelvis was recognized and significant cephalopelvic disproportion considered, the abnormal fetal axis due to laxity of the abdominal wall seemed also to be a factor. Accordingly, an abdominal binder was applied, and from that moment labor progressed rapidly and successfully. The infant weighed 2300 grams.

Discussion

See Discussion after Case No. 321.

Case Report: ABNORMAL AXIS OF LABOR FORCES DUE TO LAXITY OF THE ABDOMINAL WALL.

Acknowledgment

This case is presented through the courtesy of Dr. Richard Rosenberg, Good Samaritan Hospital, Suffern, N.Y.

CASE NO. 321

A 28-year-old gravida II para was at term in early labor following spontaneous rupture of membranes. Late pregnancy had been complicated by severe pelvic thrombophlebitis requiring anticoagulant therapy. Obstetrical progress was slow and the fetal head remained high. Pelvimetry was requested.

Pelvimetric measurements were within the normal range. In the standing lateral projection, the fetal head was high, just dipping into the pelvis, and the fetal spine and occiput were directed anteriorly. The placenta was located high on the posterior wall. A 10 cm diameter soft tissue mass was identified above the pubic symphysis and anterior to the fetal head and neck. The mass was convex superiorly, smooth in outline, and separate from the uterine wall (Fig. 1). The diagnosis of a distended bladder was suggested.

Clinically, a smooth mass was palpated above the pubic symphysis. The patient was catheterized and the mass disappeared. The fetal head descended and labor progressed rapidly and successfully.



Case 321, Fig. 1. Standing lateral projection from pelvimetry examination reveals a 10 cm smoothly outlined mass above the pubic symphysis anterior to the fetal head and neck (arrows). The mass is convex superiorly and separate from the uterine wall; its lower margins are not identified. The fetal head is high, just dipping into the pelvis.

The radiograph was exposed to delineate the placenta, which was located high on the posterior wall (not shown). The vertical line running through the film represents the edge of a piece of plain paper placed anteriorly in the cassette between the film and one of the intensifying screens, in order to equalize the radiographic exposure through thick posterior and thin anterior parts.

Discussion

These cases illustrate practical clinical points with "cute" radiographic findings. In Case No. 320 there is a graphic demonstration of an abnormal axis of labor forces. While the lordosis, scoliosis, and small pelvic measurements were important contributory factors, the laxity of the abdominal wall and the nearly horizontal fetal axis were determinant and labor was unsatisfactory. Simple application of an abdominal binder resulted in a successful labor.

It is certainly widely appreciated that lower bowel and bladder contents can obstruct, impede, or complicate a vaginal delivery, and the clinical features in Case No. 321 merely serve to remind us of this well known concept. However, it is unusual to demonstrate this point radiographically; also, it is of interest to demonstrate the effect of pressure on the distended urinary bladder as it accommodates itself to encroachment by the fetal head. We have seen a similar effect produced by other large pelvic tumors in the female. Radiographic differential diagnosis here must include other pelvic tumors, such as ovarian masses and uterine fibroids, displaced upwards out of the pelvis by the gravid uterus, and also tumors of the lower abdominal wall. Identification of uterine and abdominal wall stripes helps in localization. Finally, if the placenta is high and no mass is identified to explain failure of the head to descend, a short cord syndrome must be considered.

Case Report: DISTENDED URINARY BLADDER IMPEDING PASSAGE OF THE FETAL HEAD.

Acknowledgment

The case is presented through the courtesy of Dr. Eugene Schwartzman, Good Samaritan Hospital, Suffern, N.Y.

CASE NO. 322

A 62-year-old man was evaluated because of gross hematuria, subsequently proved on cystoscopy to be due to hemorrhagic cystitis. Intravenous pyelogram and infusion pyelogram with laminograms were performed (Figs. 1 and 2). No intrinsic abnormality was noted in the upper urinary tracts. An incidental finding was the demonstration of the renal fascia.

Discussion

The renal fascia is a layer of connective tissue which envelopes both the kidney and the adrenal in a common sheath. Although somewhat unusual, the fascial layer can be seen normally on simple film study by virtue of the presence of a thin layer of fat between it and the renal parenchyma. One would predict easier and more consistent delineation with tomography (Fig. 2), and it is regularly demonstrated with perirenal air insufflation. As has been pointed out, its visualization may be helpful in differentiating renal-adrenal



Case 322, Fig. 1. Anteroposterior abdominal radiograph 15 minutes after intravenous injection of contrast material reveals no intrinsic abnormality in the urinary tracts. A thin white line parallels segments of the renal contour on each side (arrows).



Case 322, Fig. 2. Frontal laminogram through the kidneys (8 cm level) following infusion of a large volume of contrast material reveals densely opacified renal parenchyma. Thin white line segments are sharper and more easily seen than in Fig. 1 (arrows). These lines represent the renal fascia, separated from the renal parenchyma by 1–2 mm of lucent fat.

masses from those originating in adjacent structures, but it cannot be used to separate renal from adrenal masses (1).

Case Report: DEMONSTRATION OF THE RENAL FASCIA.

Reference

1. Whalen, J. P. and Ziter, F. M. H. Jr.: Visualization of the Renal Fascia—A New Sign in Localization of Abdominal Masses, *Radiology* 89:861–863, 1967.

CASE NO. 323

A 20-year-old man was struck behind the right ear by a board and sustained a puncture wound in the posterolateral suboccipital region of the right neck. During the next week the patient complained of increasingly severe headaches and physical examinations revealed meningismus, minor reflex changes, and questionable blurring of the optic disc margins. Clinical impression was that of cerebral concussion, with subdural hematoma to be excluded. Percutaneous right carotid angiogram was performed and was somewhat limited technically but no gross abnormality was demonstrated. Lumbar puncture was performed and bloody cerebrospinal fluid was obtained. A bruit was heard in the right mastoid region.

Right brachial angiogram was performed (Figs. 1a, 1b, and 2). A large plexiform and racemose collection of vessels appeared in the course of the



Case 323, Fig. 1a. Early radiograph from the frontal series of a right brachial angiogram shows opaque material filling the subclavian artery in retrograde fashion and good filling of the vertebral artery.



Case 323, Fig. 1b. One second later, the entire right internal jugular vein is opacified (arrow). A racemose arteriovenous fistula is partially obscured by the mastoid bone and the angle of the mandible.



Case 323, Fig. 2. Early radiograph from the lateral series of a right brachial angiogram has been subjected to second-order subtraction technic. The carotid artery is well opacified anteriorly and the vertebral artery is poorly opacified posteriorly and exhibits a streaming effect. Between these two vessels there is moderate opacification of the internal jugular vein (vertical descending arrows overlie the vessel and point in the direction of flow). A large plexiform and racemose collection of densely opacified vessels lies posteriorly in the course of the vertebral artery (posterior arrows).

vertebral artery near the skull base. There was early filling of the internal jugular vein from the level of the transverse sinus to the superior vena cava. The terminal end of the vertebral artery and the basilar artery were not opacified. The radiographs were reproduced with subtraction technic; although many of the smaller vessels were clarified, the exact site of abnormal communication between arterial and venous trees could not be identified. The diagnosis of traumatic arteriovenous fistula was suggested involving vertebral

artery and adjacent venous structures with drainage via the internal jugular vein.

The patient's clinical condition remained stable. Left brachial angiograms filled the left vertebral and basilar arteries and the terminal end of the right vertebral artery, but the fistula was not opacified. Surgical ligation of the right vertebral artery in the neck failed to eliminate the bruit and a second surgical procedure was performed. The right vertebral artery was again ligated proximal to the fistula in the neck, but in addition the vessel was also ligated distal to the fistula at the base of the skull via occipital craniotomy. The bruit disappeared and angiography performed in the operating room failed to opacify the arteriovenous fistula.

Discussion

See Discussion after Case No. 324.

Case Report: TRAUMATIC VERTEBRAL ARTERIOVENOUS FISTULA.

Acknowledgment

This case is presented through the courtesy of Drs. Marvin Shapiro and Joseph Polifrone, Good Samaritan Hospital, Suffern, N.Y.

CASE NO. 324

A 19-year-old boy sustained head trauma 8 months prior to admission with multiple fractures of the facial bones and skull. One of the fractures crossed the sella turcica at the base of the skull to enter the sphenoid sinus and allowed a small amount of air to enter the cranial cavity (Fig. 1). In the few months prior to admission the patient experienced several nosebleeds of increasing severity. Also, there was gradual loss of visual acuity in the left eye which progressed to total blindness. There was no proptosis.

A major nosebleed precipitated his admission to the hospital and multiple blood transfusions were required; nasal packing did not control the bleeding. Ligation of the anterior ethmoidal artery followed by ligation of the external carotid artery were performed, but major bleeding recurred.

Left carotid angiogram was performed. An arteriovenous fistula was demonstrated between the carotid artery and an ophthalmic vein with aneurysm formation in the vein (Figs 2a-d). The location of the fistula correlated well with the fracture previously demonstrated (Fig. 1); the location of the aneurysm correlated well with the progressive visual loss.

Although other vascular diagnostic studies were scheduled, a major nosebleed supervened and ligation of the left common carotid artery was performed. Except for one major nosebleed in the immediate postoperative period, no further major bleeding occurred.

Right carotid angiogram performed four days postoperatively opacified both anterior cerebral arteries but the fistula and the aneurysm were not visualized.



Case 324, Fig. 1. Lateral radiograph of the skull following head trauma reveals a fracture line crossing the mid-portion of the sella turcica and entering the sphenoid sinus (lower arrow). The sinus is opacified. A small collection of air lies within the skull just above the posterior clinoid processes (upper arrow), tell-tale evidence of fracture into an air sinus.

Left brachial angiogram performed two weeks postoperatively opacified the posterior circulation, posterior communicating artery, middle cerebral group and the ophthalmic artery, but the fistula and the aneurysm were again not visualized (Fig. 3). The patient stated at this time that shadow vision had returned to the left eye, but there was no further return of function one month later. Nosebleeds had ceased.

Discussion

The two cases presented are interesting examples of traumatic arteriovenous fistulae and their complications. The clinical features of Case No. 323 emphasize the rapidity with which the abnormal communication can become symptomatic, and also the magnitude of the racemose collection of associated vessels. These facts suggest that a sizeable high pressure shunt was created at the time of the initial insult. From the surgical viewpoint, best results are



Case 324, Fig. 2a. Early radiograph from the lateral series of left internal carotid angiogram reveals a tiny "squirt" of opaque material directed anteriorly from the anterior aspect of the infraclinoid carotid artery (arrow). The ophthalmic artery is seen just superior to this point.

obtained when the fistula can be isolated by ligation of the major proximal and distal connections, but a significant failure or recurrence rate exists even when this appears to have been accomplished.

Case No. 324 is quite unusual since most post-traumatic fistulae in this location are between carotid artery and cavernous sinus. Even when the radiographs in this case were subjected to subtraction technic, opacification of the cavernous sinus could not be demonstrated. Since the ophthalmic veins drain directly into the anterior end of the cavernous sinus, and with all the venous structures closely applied to and virtually surrounding the carotid artery, a discrete carotid artery—ophthalmic vein fistula must be extremely rare. The presence of pneumocephalus is an important radiologic sign, in this case indicating fracture into an air sinus. Epistaxis as the presenting symptom of aneurysm in this location has been reported (1, 2).

Case Report: POST-TRAUMATIC ARTERIOVENOUS FISTULA BETWEEN CAROTID ARTERY AND OPHTHALMIC VEIN.



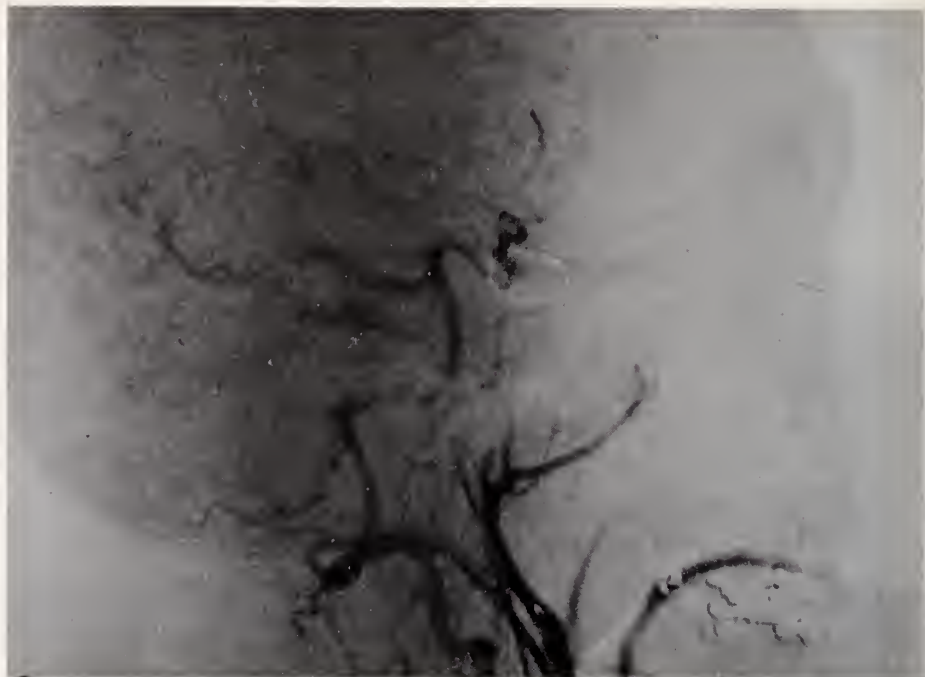
Case 324, Fig. 2b. One-half second later there is opacification of a large aneurysm which lies just inferior to the ophthalmic artery (arrows), the result of fistula between the carotid artery and an ophthalmic vein.



Case 324, Fig. 2c. A few seconds later the aneurysm remains opacified during the venous phase (arrows). The cavernous sinus is never opacified. The nasopharyngeal soft-tissue shadow is extremely wide as a result of a large amount of packing material. Surgical clips anteriorly are in the nasal cavity from previous ligation procedure.



Case 324, Fig. 2d. Early radiograph from the frontal series in late arterial phase reveals the aneurysm located close to the midline (arrows). In this position, the aneurysm reaches the nasal cavity and indicates compromise of the medial-posterior wall of the orbit. Surgical clips in the nasal cavity anteriorly are again seen (arrow A).



Case 324, Fig. 3. Lateral radiograph from left brachial angiogram (8 seconds after injection) has been subjected to subtraction technique. The posterior circulation is opacified but not the internal carotid artery. Opaque material enters the anterior circulation via the posterior communicating artery and fills the middle cerebral group. The ophthalmic artery is visualized (circle) but the aneurysm is never opacified.

Acknowledgment

This case is presented through the courtesy of Drs. John Sadowski and Sheldon Katz, Good Samaritan Hospital, Suffern, N.Y.

References

1. Busby, D. T., et al: Fatal Epistaxis via Carotid Aneurysm and Eustachian Tube, *Arch Otolaryng* 87:295-298, 1968.
2. Voris, H., and Basile, J.: Recurrent Epistaxis from Aneurysm of the External Carotid Artery, *J Neurosurg* 18:841-842, 1961.

EDITOR'S NOTE

On October 20th, 1968, the Mount Sinai School of Medicine of the City University of New York was dedicated, and Dean George James of the School of Medicine was installed as first president of the Mount Sinai Medical Center. The day-long exercises with the general title, "The Future of Medicine and Its Relationship to Society," had as their intellectual high point the series of four addresses which follow, delivered by four Nobel Laureates, each world-renowned in his special field, all sharing a common interest in humanity and in the humanities. Each has bridged the gulf between the two cultures of which C. P. Snow has written. Each address is evidence of how much a part of both cultures the speaker is. We hope that those of our readers who were not privileged to have heard them in person will enjoy reading their provocative and stimulating philosophical observations.

Medicine in a Changing World

DR. GEORGE W. BEADLE*

I am deeply honored and pleased to have a small part in the dedication of this magnificent new Mount Sinai School of Medicine-Medical Center and in the inauguration of its new President, George James. I bring special greetings from the Pritzker Medical School, the Medical Center and their parent institution, the University of Chicago. You have paid us great honor by looking longingly at some of our faculty members. We do not object, for we believe free competition has been largely responsible for the fact that this nation has an especially strong system of higher education including medical education.

We share many sympathies, one arising from the fact that we both exist in and near central city communities in which are found many of the most urgent and difficult social problems of our time. We at Chicago have not evaded them by moving away from them as some less courageous institutions have. This dedication, and the inauguration, are persuasive evidence that you too are prepared to face them and to do your part in helping solve them.

If our major universities, including their medical schools and centers are not willing to do this, who among us can be expected to?

As the world changes, so do medical science and medical practice—both at increasing rates.

I assume my fellow speakers will review and evaluate the remarkable advances in basic science that so importantly contribute to medicine, and in which they themselves have played such significant roles.

I propose to speak mainly about the role a university can and should play in making the benefits of modern medicine maximally available to the many and diverse segments of today's society.

*Nobel Laureate, Medicine and Physiology 1958. Institute for Biomedical Research, A.M.A.

I apologize in advance if in doing this I seem to be diverted in two directions that may not at first seem clearly and immediately relevant.

First, I shall speak more broadly about social problems and ills, for I am sure we all agree that those faced by modern medicine must be attacked and solved in a very broad context.

Secondly, I shall refer frequently to my own university, even if in so doing I appear to be immodest and provincial.

I do the latter for several reasons:

I know more about my own institution than I do about any other.

The University of Chicago is unique in many respects related to the general problem.

And it has participated actively and effectively in a number of social experiments and demonstrations that I believe have special significance. Perhaps my immodesty will be somewhat muted by the fact that most of these were made before my time as President of the institution.

As background I wish to review a few facts about the University of Chicago and its adjacent communities that bear directly on our broader theme of the day.

I begin with the University.

It was founded 76 years ago, unlike most of its counterparts, initially as a full-fledged university with a college, a normal complement of graduate departments and a beginning toward a professional school complex. Initially it had no medical school, although it had great strength in the underlying science disciplines, and early in its history graduated many students who later went into medicine.

Despite the name Chicago, the University is private and receives no general and unrestricted support from either the city or the state.

It has always been small; now has 8500 students, two-thirds of them at the graduate level.

It was the first university I know of to establish a department in the field of sociology.

Although responsible for many significant innovations in higher education, the history of the University was relatively free of trauma during its first half century. Later, problems began to multiply ominously.

Its island-like location eight miles south of the City's business center, close to Lake Michigan and with parks on two sides, has profoundly influenced this more recent history. For prior to, during and immediately after World War II the neighborhoods adjacent to the University attracted large numbers of unskilled meat-packing, war-industry and other workers, many of them Negroes from the deep south.

As a result of this influx and the war-time freeze on building and rehabilitation, the two square miles to the University's north plus the square mile to the south, just across the Midway Plaisance, where most faculty members, staff and students had from the beginning lived, became drastically overpopulated and physically deteriorated. During the post-war period, crime

increased frighteningly, students decreased drastically in numbers, many faculty members left the University and a high proportion of non-academic staff moved from these immediate areas. The very survival of the University was seriously threatened.

With invaluable advice from the University's sociologists and other knowledgeable and concerned persons, the community leaders in Hyde Park-Kenwood (the one to the north), the City of Chicago, and the University set about the unprecedented task of renewing the community and restoring confidence. Many said it had never been done and that it was a hopeless undertaking.

But eighteen years of sustained effort have produced dramatic results, even beyond the hopes of some of the most optimistic participants.

Hyde Park-Kenwood is now the most successful example of a socially and financially stabilized interracial community I know. The population was reduced from a peak of more than 70,000 to its original 55,000. Dwellings were upgraded. New construction has been extensive. Some 300 million dollars in private capital have been invested. Public housing in small scattered architecturally diverse units has been voluntarily accepted, has been built, and has now become such an integral and responsible part of the community that even its nearby neighbors do not identify it as *public housing*. Hyde Park-Kenwood is now highly diverse in many respects: racially (40 per cent non-white), ethnically, religiously, economically, educationally, occupationally and culturally. More than 70 per cent of the University's faculty members live in the community within easy walking distance of the campus.

Although there remain many problems to be solved, some of which are now greatly intensified by recent trends and unrest among people in adjacent neighborhoods, and by some students, I believe it is entirely fair to say that Hyde Park-Kenwood has accepted and, to a very considerable extent, solved its fair share and more of the major social problems that now face the nation.

If every other community in the nation were to do as well, I am convinced that a large fraction of our most urgent social problems would cease to exist.

Unfortunately, the Hyde Park-Kenwood undertaking was so costly in time, money, and effort that it could not at the time be extended to the square mile to the south of the University that is a part of the community called Woodlawn. As a result, Woodlawn has undergone almost complete racial transition and is now nearly 100 per cent Negro. It is characterized by substandard housing, an unskilled work force, high unemployment, inadequate educational preparation and facilities, high crime and delinquency rates, inadequate recreational and cultural opportunities, and woefully substandard medical facilities and service.

Many members of the University have recently begun working actively in Woodlawn in an attempt to identify and solve major problems, including those attributable to inadequate medical services.

First, let me speak about the general approach.

It has become abundantly clear that the only effective approach to prob-

lems in such a community is through urging the community itself to both recognize its problems and to take some initiative in attempts to solve them. I want strongly to emphasize this last point. Time after time we have seen it demonstrated with crystal clarity that communities with serious social problems do not want solutions imposed from without. Deep resentment is almost always the result. Confidences must be won. Change must be wanted, and help in bringing it about welcomed. It is not easy to say how this should be brought about, but it is clear that it is essential.

If we at the University of Chicago have learned anything, we have learned that.

It follows that a university can be maximally effective if it uses its resources to advise, to help collaborate in research projects designed to solve specific problems, and to aid in setting up model or demonstration operations that point the way toward solutions on a broader front.

To this end, the University of Chicago, through its Urban Studies Center has, at the invitation and request of the Woodlawn Organization (known as TWO), established a number of special task forces. Each of these includes both University faculty members and students, and each works in close collaboration with a counterpart task force from the community, through TWO.

These task forces worked industriously last summer on the following problems:

- Housing and Environment
- Employment and Commercial Development
- Education
- Welfare
- Legal Rights
- and finally, Mental and Physical Health

The work of these groups will provide a basis for a Model Cities proposal under the Federal Demonstration Cities and Metropolitan Development Act of 1966, which specifies that any such proposal will be eligible for federal assistance only if it provides for widespread and meaningful citizen participation in all its phases.

I should add, somewhat parenthetically, that the United States Office of Education has separately made substantial funds available for a thorough study of the public school system at all levels in Woodlawn. In this the Woodlawn Community, the Chicago public school system and the University of Chicago, through its School of Education, collaborate on a balanced three-way basis. The project is well underway under the supervision of a faculty member on leave and working with a tripartite board representing the three participating parties.

The prospects for genuine progress look bright.

Let me now, at last, turn more specifically to our involvement in community medical problems. I did want you to know the foregoing general background in which our activities in community medicine are being carried on.

Again, to provide a setting, I shall briefly describe the characteristics of our particular Medical Center.

The present Medical School was established in 1927 with substantial support from the Rockefeller Foundation and its closely related General Education Board. In formulating general policy our Medical School followed the famed Flexner Report in adopting the policy of group practice by a full-time clinical faculty unencumbered by outside private practice for supplementing income. The operation was at first strenuously objected to by the Chicago Medical Society on at least two grounds: (1) group practice by a corporate organization, and (2) unfair competition in accepting patients for teaching and research without fee, and outpatients at \$4.00 for a first visit and \$2.00 for each subsequent one. I hastily add that the fees are now considerably increased. The Society threatened expulsion of participating University faculty members and actually prohibited their giving scholarly papers before the Society meetings for a number of years.

Today our Medical Center owns and manages ten distinct but physically interconnected hospitals which share common services and facilities that are appropriately provided. In addition, the Center operates the Argonne Cancer Research Hospital under contract with the Atomic Energy Commission.

In contrast to earlier days, all patients are now available for teaching purposes and the entire hospital and clinical complex, excluding the Argonne Hospital, is financially self-supporting, including reimbursement of faculty salaries on the basis of time spent in patient care.

The full-time policy as interpreted at Chicago naturally encourages research on the part of medical faculty members. I illustrate this by a story of a visitor who, on hearing a surgeon from the Argonne Hospital report on his work, said:

"That is the most amazing thing I have ever heard. Here is a surgeon who talks like a chemist, a physicist and a mathematician."

Aside from a tremendous number of regular patients (18,500 each year) and those who are taken care of in the Emergency Service (another 35,000 annually of the latter, many of whom are unable to pay even a very modest fee), we participate in other community medical projects in several ways.

Like many other communities of its kind, the 80,000 families in greater Woodlawn have far fewer than their proportionate share of the thousands of medical doctors in Chicago. The community keeps growing in population but private physicians continue to move away from it—a decrease of about 35 per cent in 15 years, and even before the exodus there were too few.

Some left for economic reasons—insufficient income; some because their patients had moved to the suburbs; and some left because they were white and feared to live and work in a black neighborhood.

A year ago, at the request of the community and in collaboration with the Chicago Board of Health and the Children's Bureau of HEW, the University

opened a child care health center in the heart of Woodlawn, making use of a rehabilitated previously-abandoned butcher shop. The center has an active and effective Advisory Board of Woodlawn citizens.

In one year 3000 patients have registered and have made 6000 visits—some 25 daily.

One moderately frequent medical problem with Woodlawn children is chronic lead poisoning from eating paint and plaster. Much progress has already been made in removing the cause as well as in treating the affected patients.

A second off-campus University-operated health facility is the Woodlawn Mental Health Clinic, established by the Chicago Board of Health and the University's Department of Psychiatry in collaboration with a Community Advisory Board as well as the public and parochial schools of the area. This center concentrates on the problems and anxieties children face in adapting to school, this in the hope that they will thereafter be able better to adapt to society in general. The objective is to see every youngster at or before the time of entering school. Last year some 8000 were seen.

I want strongly to emphasize that despite their great importance in pointing the way toward effective larger scale solutions, University-operated demonstrations such as the two I have briefly described, cannot themselves solve the medical problems they find.

To paraphrase our own Doctor Alfred Dorfman, who heads Pediatrics at the University:

The number of people who can be served by medical schools in this way is only a tiny fraction of the total number in need.

The medical personnel available to medical schools for this purpose is only a small part of the number needed.

Society is unlikely, in the foreseeable future, to finance operations of these kinds on the scale needed. They *are* expensive.

Dr. Dorfman has proposed, as one reasonable model of medical care, that population areas be defined and designated in which medical needs can be reasonably served through group medical practice units associated with community hospitals.

Such units could be organized so as to make effective use of new types of medical personnel, trained especially to supplement the short supply of physicians which can be expected for many years in the future. Some units of this kind now exist. They need to be created in greatly increased numbers and in urban areas where they are not now economically feasible.

A number of such groups, including their community hospitals, could then enter a collaborative association with a major medical center with provisions for referral of unusual problems that require special talents and costly facilities. Referral of appropriate cases in the reverse direction—that is, to the smaller community units—could significantly reduce the load on the larger medical centers. The medical centers could also provide for continuing education of physicians in affiliated community units. The units in turn could participate in

the education of medical students, interns and residents, to the advantage of all concerned.

The problem of fair and equitable distribution of the best medical services that present knowledge permits will be difficult under any foreseeable circumstances. The continued existence of Woodlawn, Watts, and Harlems make it enormously more so than it need be. Surely the basic solution requires that we disperse, dilute and cure the concentrated social and medical ills of such communities.

White-imposed racial segregation and intolerance have created them. I am very much afraid that just as we begin to see some hope of reducing intolerance in this one direction, black separatism may counteract and even reverse the trend. If so, additional Hyde Park-Kenwoods, such as have been created in Chicago and in a few other places, will be even more difficult to bring about.

We must not give up, for there is so much to be done and so little time to do it.

Molecular Biology and Medical Research

DR. FRANCIS H. C. CRICK*

I want to take a rather different topic from Dr. Beadle. My subject is molecular biology and medical research. I am going to widen it slightly and talk about molecular biology, cell biology, and medical research. My knowledge of these three topics is very different. I have worked for many years on molecular biology. Recently I have been trying to learn something about cell biology, but about medical research I know very little.

My theme is that fundamental work in biology is going to have an increasing impact on medical practice. I am sure you are all fairly familiar with this idea, but I want to develop it with a reasonable amount of scientific content. In a certain way we can see that this is acknowledged already by considering the four speakers who are going to address you today, not one of whom is medically qualified. I am in origin a physicist. Dr. Pauling is a chemist and the other two speakers are biologists. I do not think that this choice of speakers is an accident but rather that it reflects the theme I want to bring out.

Let me first say what I mean by molecular biology. This is, of course, a portmanteau word, including a lot of biochemistry, genetics, physical chemistry, and related subjects. At the present time the word is used in two rather different ways. In the first usage it has a rather general meaning and covers all the ways in which you can think about a biological problem in molecular terms. The second meaning is rather more limited and covers in particular that part of the subject which has advanced rather rapidly. Biologically it deals with genes and gene products. Chemically it means nucleic acids and proteins and their synthesis. I shall use the latter of these two meanings. One of the characteristics of this sort of molecular biology is that the people working in it were studying properties common to *all* biological systems. They did not mind particularly, therefore, which organism they worked on provided it was convenient, and would often choose microorganisms, as was done by Dr. Beadle in his classical work.

The general ideas must be very well known to all of you. The most basic idea is that biological information is mainly carried by the sequence of side groups on the regular back-bone of a macromolecule. Genetically it is carried by nucleic acid, but many such sequences can be translated into the amino acid sequences of proteins by special and rather elaborate pieces of biochemical machinery. Another important idea is that the complicated three-dimensional structure of a protein is formed by folding up its rather simple linear chemical structure to give a molecule with a definite shape and in many cases a highly specific catalytic activity. I think everyone would agree

* Nobel Laureate in Medicine and Physiology, 1962. Member of the staff of the Medical Research Council Laboratory of Molecular Biology, Cambridge, England.

that rather rapid fundamental progress has been made in these topics in the last fifteen or twenty years. This has been underlined very recently by the announcement of the award of a Nobel Prize for medicine and physiology to Nirenberg, Khorana, and Holley for their work in this very field; that is, on the genetic code and on the structure of transfer RNA.

I think it is useful to ask why classical molecular biology has advanced so rapidly. I believe there are three main reasons. The first reason is that we were very fortunate in having a well-defined theoretical framework from which we could predict, to some extent, what was likely to be discovered. Of course, the detail character could not always be foreseen, but one had a general idea of the outline to be expected. This theoretical framework was provided in the middle fifties. The main reason this was possible is the nature of nucleic acid molecules, the functions of which are rather limited. This helps in constructing theories, because the easiest way to make a theory is to impose a restriction of some sort, and it was such a restriction which helped to give us the theoretical framework. One quite serious mistake was made. The ribosomal RNA was mistaken for the messenger RNA but fortunately this error was discovered fairly quickly.

My second reason is, I think, really the most important one: during this period there were available very powerful experimental tools for tackling these problems. I will mention a few of them, although they are all very familiar to you. For example: chromatography, both paper chromatography and column chromatography; the ultracentrifuge—not only the classical method developed by Svedberg but also the more modern usages, such as sucrose gradients and caesium chloride density centrifugation. These are techniques which one can use every day and can be applied to a wide variety of problems. Then again the electron microscope has proved a very powerful tool, although it is not the instrument of choice for getting down to atomic details. It is really best at the level of size immediately above the atomic level. One can think, for example, of the demonstration of circular DNA and a lot of modern work on the structure of viruses. For the atomic level itself the method of x-ray diffraction, applied to crystals of macromolecules, has turned out to be very powerful, especially when combined with very fast computers and automatic data collecting.

My third reason is of a totally different type: it might be described as the romantic appeal of the subject. I think it is true that molecular biology, operating at the border-line between the living and the non-living, and dealing with this difference in a very fundamental way, has attracted into it many people for just this reason. Quite a number of them were influenced by a little book by the physicist, Schroedinger, called "What is Life?" I certainly was, and I know that both Watson and Benzer also read it. There are, of course, many reasons why people go into a particular field of work and study a particular research problem. It may be because their professor has suggested it to them, or because it is fashionable (that is to say, the subject is moving rapidly and the techniques are easily available) but this particular

reason—the romantic appeal of the subject—should not be overlooked. To give an example from quite a different branch of science, I think it is often the reason why people go into such fields as astronomy and cosmology.

The next question we have to ask is: Has classical molecular biology already had important medical applications? I think the short answer to this is no. So far direct applications have been rather few. There has been nothing as spectacular or as useful as, say, penicillin. Nobody would deny that molecular biology has not already been helpful in certain lines of medical research. For example, the preparation of antibodies to a virus is certainly easier if one understands the different functions of the protein component and the nucleic acid component. Then again, the amino acid sequences of antibodies is giving us some insight into the sort of ways in which the body can produce the immense variety of antibodies which it needs. The ideas of molecular biology have also been useful in casting doubt on certain theories which one could see would be unfruitful. For example, Burnett's early theory of antibody formation violated an idea called the Central Dogma*, which says that one cannot translate backwards in detail from a protein sequence to the corresponding nucleic acid sequence. This cleared the way for his later much more interesting theory which is the dominant one today. The recent work on viral transformation (the transformation of a cell when infected with a cancer virus) could hardly have reached the sophistication it has without the knowledge and methods of molecular biology. Most people would agree that this is one of the most active and promising fields in cancer research at the present time.

There are a few examples which have a more immediate medical application. It has been much easier to accept the existence of drug-resistant episomes (which carry drug resistance from one bacteria to another) because of the fundamental knowledge of similar phenomena acquired by molecular biologists.

Nevertheless, when we look at the things one might hope to have achieved using some of this basic knowledge, such as, for example, a cure for cancer, or for various heart disorders, we must admit that so far there has been little in the way of dramatic medical applications. I think it is important to realize this. And so one has to go on to the next question: why is molecular biology important to medicine? I think it is important for two reasons. In the first place, it provides a very solid framework of fundamental facts and ideas at the molecular level for the whole of biology. The most useful comparison to make here is with the early development of chemistry. For example, the understanding of the tetravalency of carbon and the direction of the four valencies in space, and similar ideas. They did not immediately produce an enormous impact on society, but as time went on, as we can see from all the manifold applications of chemistry in the modern world, this

* The Central Dogma does *not* state that *errors* in translation or transcription cannot be caused by changes to certain proteins (or to transfer RNA). The views of Dr. B. Commoner on this point are not widely accepted.

knowledge began to be increasingly exploited and, in fact, somewhat taken for granted, so that we sometimes forget that it is a necessary basis for modern industrial chemistry.

The second reason I have already mentioned. It is the provision of very powerful experimental techniques. I would emphasize that these techniques are not something static. The nature of the subject is such that they are continually being added to and what is even more remarkable the techniques are getting faster all the time.

We had a dramatic instance of this in our laboratory this summer. As you know, Dr. Holley got his recent prize for the first determination of the sequence of a transfer RNA. This involved two steps: the fractionation of the RNA (which can take a considerable time) and then the actual determination of the sequence. Both these steps proved very difficult and the skill and persistence of Dr. Holley and his team has been rightly recognized by the award of a Nobel Prize.

This summer a young visitor to our laboratory, Moshe Yaniv, working with Mr. B. Barrell, determined the sequence of the valine tRNA from *E. coli* in a period of three months, though admittedly the material had previously been fractionated for him.

An even more striking example has been the determination, to 3.5 Å, of the three-dimensional structure of the protein elastase in our laboratory by a research student, Mr. D. M. Shotton, working under the supervision of Dr. H. C. Watson, after only one man-year of work. Shotton, who is in origin a protein chemist, hopes that he may have both the primary sequence and the tertiary structure finished for his thesis.

We have a saying in our laboratory that the difficulty of a project goes from "Nobel Prize" to "M.Sc." in about 5 to 10 years! This shows you the very rapid acceleration of techniques which is coming about.

Having discussed the nature of molecular biology and some of the reasons for its success, we must now turn to consider its future. This is always a hazardous operation, but I think we can safely make a few general predictions. In the first place, we are likely to see a fairly massive consolidation operation. Although we know the answers to many problems of molecular biology in outline, we do not yet know them in detail. For example, we do not know in detail, even at this stage, how DNA replicates. Filling in of all this biochemistry will take a large amount of work and will involve a large number of people. We can already see this process going on.

In addition, we can expect an invasion from what used to be called the more exact sciences, such as physical chemistry. Already many physical chemists are entering the field and it is likely that many more will do so, not only so that we can study structure faster and better, but also to explore chemical mechanisms.

We are also likely to see the fairly rapid extension of work to adjacent areas of molecular biology. In many of these research has been going on for some time, but we may now expect to see a greatly increased effort. One such

field, for example, is the structure and function of membranes. This is not only important because membranes occur almost universally in biology, but also because of the very many different processes which are associated with membranes. To give one example, they are of great interest for anyone studying the nervous system.

There are, of course, a number of areas which are already being intensively studied. One could mention oxidative phosphorylation and the structure of mitochondria as an example of a field which is already fairly well populated. The same might be said of a number of topics which are relevant to only part of the biological kingdom: such fields as photosynthesis on the one hand and muscle on the other. Here again there has been a fairly considerable effort over the past decade, although there are many mechanisms which are still not understood in atomic detail. One would hardly be surprised if research on animals usually turned out to be more relevant to medical problems than research on plants.

However, it is not these particular problems that I want to draw your attention to today. I think what is of more interest is the fact that the techniques and ideas of molecular biology are going to be increasingly applied to *cell* biology. The distinction between cell biology and molecular biology is somewhat arbitrary but I hope it will be clarified by some of the examples I am going to give you. So we must now turn to cell biology and see how that stands today.

Cell biology has a long and distinguished history. Interesting things have been discovered at a fairly steady rate over rather a long period, but I would prefer to look at the subject in a different way, and inquire what fraction of what we would like to know has already been discovered. If we ask ourselves this question, I think it is clear that cell biology still has a long way to go, and consequently is a field in which strikingly important discoveries are likely to be made.

Let me give a few examples from recent work. Much of what I am going to mention has been done on small mammals. With one or two exceptions they have not yet been done on man, but as we know, it is often not a very big step from mammal to man. I think many people have been surprised by the recent work, pioneered by Ephrussi and by Harris on the fusion of cells, even cells from different animals. Cells can be fused together so they will survive at least in tissue culture, though naturally it has not been possible to produce hybrid animals in this way! The properties of these fused cells are of very great theoretical interest. At the next level of organization we should remember the fusion of early embryos, done by Beatrice Mintz. This process, which has been repeated many times, does indeed produce "hybrid" mice, which, in many cases, are perfectly capable of having offspring. For example, by starting with one early embryo from a black mouse and one from a white mouse, she has been able, by fusing them, to produce a zebra mouse. This seems to me a most striking and promising technique.

Another dramatic piece of cell biology has been the transplantation of

nuclei from one cell to another, and especially into egg cells. This work was started by Briggs and King using amphibians and in recent years has been exploited very beautifully by Gurdon. Originally the technique seemed to be very difficult, but it seems that with experience people are getting more skillful at it. The application of such a technique to human beings would raise very disturbing problems for us.

Then again, for example, one should remember those experiments in which it is possible to change an adult animal, so that part of its tissues have come from another individual. This can be done if the immune response has been knocked out by x-rays, or some similar device. Under these circumstances bone marrow cells of another individual can colonize the marrow of the irradiated animal. I think these examples will give you some idea of what I mean by cell biology.

The main impression I want to leave you with is that cell biology is a field in which dramatic experiments of the above type are likely to be made fairly frequently in the near future. I doubt if this is still true of molecular biology, at least of the classical part of the subject, where I think most of the work will be more in the nature of a consolidation of what we know in outline already.

It is therefore clear that the next question we must ask is: Where is cell biology going? If we look around and see what is already happening I do not have much doubt in my mind as to where most of the effort will be placed. I think it will go into embryology. It seems to me that this field is ripe for scientific development at the present time. As you can see, many of the examples I have mentioned are very relevant to problems in embryology.

It is probably not possible to make an exhaustive catalogue of the general problems which embryology faces, but we can certainly consider the main ones. For example, how are genes turned on and off? Of course, in microorganisms we do have some idea of how this happens and we hope before long to know in some detail. When we come to consider mammals we can only guess what mechanisms are likely to operate. Then we have the problem of how cells communicate. Here again, we know that they communicate in some cases by hormones. We know a lot about the chemical structure of hormones. We know a certain amount about the action of hormones, but there is clearly very much that needs to be discovered before we can say that we understand it in molecular detail.

Then there is a whole class of molecules which have hardly yet been discovered, which I would call gradient molecules. These are the molecules whose concentrations are probably responsible for controlling the shape of an organism, and which help to decide, for example, that we should have a thumb and four separate fingers on each hand. This is indeed a very difficult field but I should not be surprised if we see dramatic progress in it during the next ten years. Other general topics would include the adhesion between cells, originally pioneered by Moseca; intercellular junctions and the study of what molecules can move freely from one cell to the next, which is being

studied by Lowenstein for example; the great problem of how cells divide, that is, the biochemistry of mitosis and what controls it; the problems of how cells migrate, not only what makes them move but also how they know in which direction to move.

For anybody wanting to enter the field of embryology, there is always the very difficult choice of which organism to study. In almost all cases man is not the ideal experimental animal, though I should mention in parenthesis that he proved quite useful in molecular biology because of his hemoglobin, mainly because there are so many physicians looking at so many patients. It seems very unlikely that we shall find a single animal which will be the best for *all* these very broad questions in embryology. It is more likely that different aspects of the subject will be best studied in different animals. For example, my colleague Sydney Brenner has already started to work on nematodes. The genetics of this is going beautifully. I think from the work he has already done it is possible to see that the genetics of nematodes could easily be worked up to the level of the genetics of *Drosophila*. These small animals have only about a thousand cells and of these a few hundred are nerve cells. It is possible to study fairly intensively the anatomy of the animal by using the electron microscope. Unfortunately, the eggs present extremely difficult technical problems and it is not clear that they are the system of choice for the study of the early embryo.

In all the various areas of cell biology there is one field which I think will attract more attention than all the rest. This is the study of the nervous system. Of all the branches of human physiology this is probably the one about which we have the most to learn. This is, of course, tied up with the fact that it is difficult. It is difficult largely because of its complexity, but we should always remember that if it were not complex we would not be clever enough to be able to understand it!

For many years there has been much interesting pioneer work on the nervous system. There is, for example, the topic of the embryology of the nervous system. How do nerves grow to make the right connections? Sperry was one of the first to do some rather dramatic experiments in this area. There has been much work on the chemical transmitters which operate at synapses and the action of drugs of various sort. A problem of a very different character is that of the overall design of the nervous system. One wonders what type of structure nervous tissue can easily be programmed to produce? We know already that what *individual* cells can do rather easily is to make proteins, but we lack the corresponding generalization for tissues. Ease of assembly must surely have an influence on which patterns of interconnections are used to carry out the various signalling operations.

There are of course many other problems. For example, what is the physical basis of memory? The fact that we cannot even give outline answers to questions of this sort demonstrates how extraordinarily little we know about the brain. Moreover, I have said nothing up to now about the behaviour of whole animals, covered by such subjects as psychology and animal behaviour.

These are disciplines in their own right but we can reasonably hope that when we understand better the mechanism of the brain the behaviour of whole animals will be easier to study.

The main thing I want to say about most of these fields is that I think they are scientifically underpopulated. How does one judge whether a field is underpopulated? I think there is a very simple test. If the classical experiments in the field have never been adequately repeated, then that field is underpopulated. The test for overpopulation is also simple. If a discovery—not necessarily an enormously important discovery, but a useful and interesting discovery—is made more or less simultaneously by three or four different groups, and if this is happening rather often, then I think it can be said that such a field is overpopulated. Incidentally, this is exactly what is happening in certain areas of molecular biology, such as protein synthesis. It is one of the reasons why it is becoming less and less fun to work on such problems, because too many people are trying to do what one is trying to do oneself.

If we apply these criteria to some of the fields I have mentioned, such as embryology and the nervous system, I do not get the impression there are many areas which are overpopulated. Moreover, if you talk to the people working in these fields, the atmosphere is very much more relaxed than in molecular biology. It may surprise some of you, who have perhaps read a dramatic book about scientific research, to know that in the early fifties, by and large, molecular biology was relaxed. When I went to work with Perutz he told me that he liked to be able to write a draft of a paper, put it away in a drawer for a couple of months and then look at it again to see how it read. Nobody ever does that now. But in these other fields one gets quite a different impression. This comes out especially when people are discussing their future work. They might do such and such an experiment this year or perhaps next year. There does not seem to be any particular urgency.

I must tell you that I think this state of affairs is likely to change. I think there is likely to be a considerable migration of people working in other fields to both embryology and the nervous system. There are good reasons for this. In the first place, there is the romantic appeal of both these subjects. Secondly, I have noticed that some of the younger pioneers of molecular biology do not wish to stay in their own subject, because they feel it is overcrowded, and in almost all cases they are moving into some branch or other of these two subjects. And thirdly, I think partly because of the influence of the techniques of molecular biology, there will be a considerable expansion of useful techniques in the near future and this itself will attract people.

It is certain that new techniques are needed. For example, consider the problem of the mapping the precise details of the nervous connections. In a piece of nervous tissue, such as the retina, this is now being done using the electron microscope, but it is an extremely tedious business. We have no methods at the moment of doing it rapidly. Certainly, here is a case where technical improvements are greatly needed, and there are very many other examples of this sort.

For the reasons I have just stated I think that these fields will soon have a large number of people working in them, using a variety of advanced techniques. As far as I can see there is only one thing lacking. In neither of these areas do we yet have a good general theoretical framework. People are trying very hard to produce ideas about both the nervous system and embryology which will have the appeal which the ideas of molecular biology had. I do not yet feel that they have been successful. We may, of course, have to face the fact that there may not be a framework of ideas which is quite as simple and easy as the one we had for nucleic acids and proteins.

But leaving this aside, I would say that both these fields are certainly set for rather dramatic advances. We should therefore turn to consider what is going to happen in the lifetime of the present medical students. How far this will take us depends on how you calculate it, but a very rough estimate shows that we have to consider the period from the present time to about the year 2000 or a little after.

I think it is clear that we may expect many striking scientific advances within this period, and that many of them are likely to have an important impact upon medical practice. In other words I am saying that the present situation, in which the impact has been on the whole rather small, is not likely to last for much longer. If the new generation of doctors is going to be able to cope with these discoveries it will clearly be important for them to have had some general background on their scientific basis to enable them to appreciate the new techniques that are likely to come along. I am very conscious that this is a problem which I am not really qualified to deal with. It seems to me to be very difficult to plan medical education so that it has sufficient grounding in the fundamentals of biology, without at the same time overloading the curriculum. Nevertheless, we have to face the fact that in the lifetime of the present generation of students this fundamental biological knowledge is going to be one of the most useful things that they could learn.

It would seem to me, as a complete outsider, that if scientific research goes on at the present hectic pace, the medical profession will have to consider seriously the question of refresher courses at periodic intervals. It may be necessary to arrange that medical practitioners have one year off in seven, as many academic people do, or one year off in ten perhaps, so that they can go back to school and be trained in the recent developments. It may turn out to be important to give many more of them the opportunity to specialise in mid-career in the new specialities that will come up. All this means, of course, that more doctors will be needed, without allowing for the fact that there are really not enough of them already.

I notice both in your country and in my own that there is a rather distressing situation. Both of us are importing too many doctors. It is true, of course, that this may be only a temporary thing, but I think it is something that people concerned with medical education should take seriously. You are going to need *more* doctors, but you are not even producing enough now. It

is for this reason that one particularly welcomes new medical schools at the present time.

Following on what Dr. Beadle said, I also notice that you will have a problem, which is not quite so serious in my own country, of the racial nature of your input. This is somewhat dramatically shown by the racial composition of the audience in front of me. It certainly does not reflect the composition of your country as a whole.

There is one other topic I should like to mention briefly. Because of the very fundamental discoveries which are going to be made, you are going to have a change in the nature of medicine. It is often said that whereas, in the past, doctors mainly dealt with people who were rather obviously ill, in the future there will be more emphasis on preventive medicine. But beyond that I think that within this period there will be a different sort of medicine coming into existence, the medicine which applies to people who are basically healthy but who want to change in some sort of way.

There already exist branches of medicine which have this character, for example, cosmetic surgery. Someone has too big a nose and thinks it would be nicer to have a smaller one. I think there will be many more demands of this sort and especially for drugs which will alter people's behaviour. Incidentally, I should tell you that in preparing this talk I did notice one rather interesting omission in current medical research. As far as I know, there does not seem to be any federal money spent on research for a good aphrodisiac. I do not believe this is because somebody in authority thinks it would increase the population rate, which might be a good reason. I suspect it is due to your puritan tradition, even though this is already changing rather rapidly. I think we may expect a demand for many drugs of this general character. For example, a drug to help people memorize things more easily. As for myself, I would particularly like a little drug which would deal with the time shift I have to suffer every time I come to your country.

I also think one is going to be faced with demands for modifications before birth. I do not want to say much about the genetic side because Sir Peter Medawar is going to deal with that topic. But if there were a technique which could produce, say, more intelligent children, I have no doubt there would be a very heavy demand for it. At the moment we know so little that it is not clear whether something like this will ever be a practical possibility.

Finally, although I only want to touch on this briefly, I think everybody realizes that many of the new discoveries will present us with very considerable ethical problems. These are of course with us already. Who should have the use of the limited number of kidney dialysis machines? When is it proper to turn off the oxygen to somebody who is little better than a vegetable? Unfortunately, there will be more and more of these problems and they will increasingly apply to people who are not really ill in the ordinary sense of the word. You already have an example of this in the contraceptive pill, which I imagine must be giving considerable trouble to Catholic doctors.

In summary, then, my prediction is that we are likely to see in the decades ahead of us an enormous development in basic biological research. During the time in which the medical students of today will have to practice, this research will have a considerable impact on what they will be doing. This means that it is important to think ahead and try to foresee how they could cope with it, not only on the medical side, but also on the ethical side.

Personally, I find these problems a little intimidating, certainly challenging, but also very exciting, and for me this is perhaps the most encouraging thing about the whole situation. Thank you.

Genetics and the Medicine of the Future

SIR PETER MEDAWAR*

The theme of our colloquium is the medicine of the future, and the question I should like to discuss, put in very general terms, is this. How far are we justified in assuming that the secular improvement in general health which has distinguished the past 100 years will continue into the future? What factors, if any, are working in such a way as to reverse the trend and impose a still greater burden on the medical service? I use the term 'medical service' to stand for all the professional, technical, and industrial agencies that are directed towards the prevention and eradication of disease, for we shall be taking far too narrow a view of things if we confine our thoughts merely to the laboratory and the hospital ward. It has become a truism, though it is none the less true, to point out that the tremendous improvement in general health that has occurred during the past century is to be attributed to the improvement of the environment far more than to the introduction of specific medical remedies.

The objective evidence of the improvements I have been referring to is to be found in the increase in the mean expectation of life at birth and (though to a steadily diminishing degree) at all later ages. It is also to be found in the advancement of the mean age of attainment of physical maturity, the increase in human growth rate, and (though again to a lesser degree) in the average final size which adults achieve when overall growth was ceased. But in the advanced industrial countries all these figures are now tending to limiting values, as less privileged members of the community catch up with the more favoured. Now therefore is a specially good time to put the questions I formulated above.

I shall be considering the future of medicine only in the advanced industrial countries. I am very well aware that the greatest and noblest task of the medical service is to extend to the world generally the privileges at present enjoyed by only a minority of the world's population, but I am going to make the comfortable assumption that in due course the less privileged nations *are* going to catch up. If they fail to do so, it will not be for medical but for political and economic reasons. If my assumption is correct, a great institution such as this should be thought of not in the worn out imagery of battlefronts and breakthroughs, but rather as a pilot plant for the future of medicine generally. What happens in this institute in the next five years will be a microcosmic version of the things that will happen in medicine in the world as a whole during the next 50 years.

If one constructs a balance sheet of factors acting for or against an increasing standard of general medical welfare, the credit entries are obvious enough and need no comment before an audience such as this. The debit entries are

*Director of the National Institute for Medical Research, London, England, Nobel Laureate in Physiology and Medicine, 1960.

of two distinguishable kinds. On the one hand we may point to new causes of mortality and morbidity, particularly accidental death, industrial disability, intoxication by waste products, diseases of addiction, and the disturbances of mind or morale that are caused by the increasing complexity and pressures of a competitive society. Superimposed on this is the stunning cost of medical welfare—an insupportable burden unless the healthy are going to help to subsidize the sick in much the same way as, in all equitable societies, the rich help to subsidize the poor. But these problems are not primarily medical in origin, and it is not necessarily to medicine that we look for a solution; we look rather to administrative, legislative, and political action.

But there is a second class of problem which is medical in origin and which calls for medical or more generally for 'scientific' solutions. For example: Is the improvement of the environment undermining our natural inborn versatility and our ability to cope with stress? Is it true that advances in medicine, by preserving the unfit, are progressively undermining the genetic constitution of the human race? What truth is there in the contention that many modern drugs substitute new ailments for those which they profess to cure? Does not the extra life that medicine brings us decline in quality as it extends in length? Does modern psychiatry really cure people, or does it merely stun people into a state of conformity to or acquiescence in a society whose practices would, many of them, be regarded as insane if judged by the canons we apply to the behaviour of individuals?

To all these questions the answer is the same. The dangers they call attention to are greatly overstated, though we can see very well why such questions should be put. But we must remember that even if the dangers are to a large extent illusory, the fears they give rise to are not illusory, and the fact that they should be voiced at all marks a complete transformation of the attitude of the public towards medicine and science. I hope you will not make the mistake of underestimating its significance. In the 19th century, it was taken for granted that science and medicine and engineering were allies of civilization. The lay public thought us in the very forefront of those who were working for the improvement of the lot of man and trying to make the world a better place to live in. This assumption is no longer made. There is even a slight presumption that we are up to mischief unless there is some clear evidence that we are going good. I myself think it by no means unhealthy that the public should adopt an attitude of vigilance or even of suspicion. If our activities are indeed beneficent, we should have nothing to fear from public scrutiny.

My particular theme is the threat that medicine brings with it the possibility of a genetic debilitation. Let me revert then to the first two questions I put to you a moment ago, starting with the idea that the improvement or softening of the environment is depriving us of our inborn ability to cope with disease, privation, exertion or stress.

At first sight it seems obvious that the improvement of the environment must have a dysgenic effect. Natural selection has been relaxed. If we live in a world, or in a microcosm, in which we are protected from infectious disease,

undernourishment and the attacks of predators; if we are no longer called upon for acute physical exertion or for anything requiring much in the way of stamina; if we are no longer exposed to extremes of heat and cold or wet and dry in a cosy air-conditioned world; why then, we *must* be taking away the natural inborn advantages of those whose genetic constitution equipped them specially well to cope with all these vicissitudes and hazards. There is therefore bound to be a deterioration, a softening up, a gradual loss of inborn ability to cope.

This argument is a very plausible one, and it is part of a powerful Puritan tradition that people should earnestly *want* to believe it. Sloth and self-indulgence should not be allowed to go unpunished; only exertion and privation can be relied upon to keep us up to the mark.

Yet, curiously enough, there is no evidence that the argument as I have outlined it to you is actually true. On the contrary, there is just a hint that it is positively *disadvantageous* to be genetically equipped to cope with dangers we are no longer exposed to. For example, the frequency of the genotypes associated with a special liability to contract diabetes mellitus is well known to be paradoxically high: Why have these genotypes not been expunged from the population by natural selection, that is by the death of those who possess them? Dr. J. V. Neel has suggested that what may be loosely called the 'diabetic constitution' may have been a positive advantage under conditions of privation or semi-starvation: The diabetic has a 'thrifty' genotype, particularly well able to make the most of a limited number of calories. If this is true, it illustrates very well the point I have just made: that it is not advantageous to be genetically forearmed against a risk after the risk has been withdrawn. On the contrary, the thrifty constitution is actually *disadvantageous* when privation has given way to an adequacy of food, because it now 'presents' in the form we recognize as diabetes.

I do not know of any evidence that inborn resistance to disease or disability of any kind is associated with a genetic constitution that is advantageous or desirable in itself, i.e., advantageous apart from whatever specific privilege it confers. The secretors of blood group A and B substances enjoy a special measure of resistance to duodenal ulceration, but there seems to be no intrinsic advantage in belonging to one blood group rather than another. The ability or inability to taste phenylthiourea seems to be associated with inborn differences in liability to ordinary nodular goitre, but it is not a credit or a reproach to us in any other way.

The point is most clearly made by inherited differences in susceptibility to infectious disease. A person who enjoys some degree of inborn resistance to a particular infectious disease is very likely to owe it to some oddity or quirk of molecular structure or metabolism which is quite useless and possibly even harmful in any situation in which he is not exposed to that particular disease. Cases in point are sickle cell trait (to which Dr. Pauling made such notable contributions), and probably thalassaemia minor. Since the inborn resistance of the heterozygotes to malaria is paid for by the lives of homozygotes, suffer-

ing respectively from sickle cell anemia and thalassemia major, it seems not too much to say that inborn immunity to malaria is purchased by a cheap genetic trick. I strongly suspect that the kind of genetic constitution that confers resistance to bacterial or mycobacterial infection generally may be useless or harmful when we are no longer at risk. If therefore we eradicate malaria, we are not conniving at a genetic deterioration of mankind. If anything we shall bring about a genetic improvement: the complete supplanting of hemoglobin S, for example, by hemoglobin A.

This, however, is only half the story. In all such cases we are dealing with the loss of genetic endowments which conferred fitness in a tough and physically hostile environment of the kind which, in advanced industrial countries, is slowly fading away, and will soon cease to exist. But what about the preservation of genes which are positively disadvantageous in the environment in which we *do* exist?

Today, sheer medical virtuosity is keeping alive people who 50, 20, and even 5 years ago would certainly have died. If the disabilities, sometimes mortal disabilities, which people are now being rescued from are to any degree 'inborn' in origin, then to precisely that degree we are clearly conniving at a genetic deterioration of mankind. For example, if phenylketonuric children who would formerly have died young or lived as imbeciles are now rescued and given an opportunity to reproduce, the frequency of the offending gene must necessarily rise, and so also, therefore, must the actual or potential frequency of phenylketonurics. How serious is this threat, and what can we do to meet it? What is our defence against the charge that a large part of modern medical practice is fundamentally dysgenic in its long-term effects?

We must not underestimate the force of this argument. There are in fact two kinds of ways in which we may cope with phenylketonuria or other highly damaging diseases of recessive determination. The first, somatic cure, is to create around its victim an environment in which the malignant gene can no longer express itself as an overt disease. The phenylketonuric or galactosemic child must live in an environment free from or low in phenylalanine or lactose as the case may be. The second, somatic prevention, is to adopt or encourage the adoption of marriage counselling procedures which will reduce the overt incidence of the disease in the first place. Nearly all overt cases of phenylketonuria are the children of parents who are both genetic carriers of the disease. If heterozygotes can be identified, then they can be warned of the consequences of marrying each other, namely that one-quarter of their children will on the average be victims of the disease, and one-half will be carriers like themselves. They should therefore be discouraged from marrying *each other*. A policy akin to this has been advocated for thalassemia major, Cooley's anemia. It is humbug to say that such a policy violates an elementary right of human beings. No one has conferred upon human beings the right to produce maimed or biochemically crippled children: it is a tragedy, and one which married couples would do their utmost to avoid. Yet whichever kind of solution we adopt, the genetic consequences will be the same. The fre-

quency of the malignant gene will steadily rise, so progressively increasing the burden from which these preventive or remedial measures are trying to relieve us. From the standpoint of genetic medicine, both 'cure' and 'prevention' are merely symptomatic. Natural selection has been relaxed (a polite way of saying that the victims of the disease no longer die), so that nothing now opposes the increase in frequency of the gene through the pressure of recurrent mutation. We are dealing here with a genetic equivalent of inflationary economics: we seem to be getting on all right, but the currency is deteriorating.

Most physicians are aware of all this as a theoretical danger, but some instinct in them prompts them to belittle it, to think that too much can be made of it, and that it will all come right in the end. In any case, their obligations are towards individual human beings. Present evils are enough for them to cope with, without taking it upon themselves to be trustees for the future of mankind generally.

My own feeling is that their instincts are probably well founded. Most amateur discussions of danger of genetic deterioration leave one important parameter out of account, the secular time scale. The rate of genetic deterioration of mankind is measured on a time scale of which the units are generations. The rate of advancement of medical knowledge is measured against a time scale of which the units are years. Because it is logically impossible to predict the character of new scientific ideas, people almost automatically tend to assume that we shall be confined to present remedies in trying to cope with future evils. But what could be more shortsighted than to assume that the medicine of the future will *not* be able to cope with future disabilities? We cannot predict what the new remedies will be, but we can identify some of the general areas in which they might be expected to fail. Direct genetic or gametic repair is not likely, but it is not inconceivable; nor is gametic selection; nor is the very early embryonic diagnosis of foetal abnormalities, particularly those that are the consequence of gross derangements of the chromosomal apparatus. These advances, when they come, will come from institutions such as this.

I therefore tend to depreciate the importance of the genetic threat to mankind which the advance of medicine could in theory bring with it. The genetic threat, however, was only one of many which are looked at by the educated lay public with foreboding. Let me therefore repeat the opinion which I expressed a moment ago. It is absolutely right that the public should scrutinize the activities of physicians and scientists, and call upon us to give a fair account of ourselves. Our work may be too specialized and technical to be intelligible, but our motives and the consequences of our actions are understandable, and it is unconditionally necessary that we should make them understood.

Medicine in a Rational Society

DR. LINUS PAULING*

My subject is "Medicine in a Rational Society." I am not sure that this is the same as the title of the symposium, "The Future of Medicine," but I hope that it is.

First, what is a rational society? I think a rational society would be a society that is based upon rational principles, or one rational principle; and this means an ethical principle. I think that the golden rule, "As ye would that others should do unto you, do ye also unto them likewise," is just such a basic ethical principle. I think that it has a rational basis, too.

You know, what is it that makes some people happy, that some people would like to do? Well, having a billion dollars, for example, or marrying someone who has a billion dollars, or being elected president of the United States of America, or even vice-president. But these goals, these ideals do not need to concern us now, because obviously it would not be possible for everyone to achieve such a goal—only a negligible fraction.

What do I want? What have I wanted during my life? I have wanted to be happy, and I am fortunate in having been happy. I have been a happy man all of my life. I have wanted not to suffer; and it seems to me that I can judge from the behavior of other people that they are like me, or perhaps I should say, that I am like them. I am a man, like other men. I think that in general people want to be happy, and I believe that I can logically conclude that it is my duty to work for the happiness of other people. Then, only then, can I expect that they would work for my happiness.

Now, when there is so much suffering in the world, we may say, as a sort of corollary of the golden rule, that the basic ethical principle should be that we should work for the minimization of the amount of human suffering in the world.

We do not have a rational society now. Our government is not dedicated to rationality, to ethical behavior. It is an immoral government, an evil government, that does not work for the welfare of human beings. It is not the only one. All governments are immoral and evil. And it is, of course, encouraging that the young people recognize this; that the young people are revolting. This spirit of revolt can give us reason to hope that we shall, in the course of time, have a rational society, and that this medical school may be able to contribute to the development of medicine for a rational society.

Medicine has made astounding progress, as Professor Medawar has indicated. There were the great discoveries that led to the general control of the infectious diseases, mainly during our own century—during the last hundred years. The progress in biology, in genetics, has been astounding. Molecular medicine is on its way. The hemoglobinemias are an example—there are a

* Nobel Laureate in Chemistry, 1954, Nobel Peace Prize, 1962. Professor of Chemistry at the University of California.

hundred abnormal human hemoglobins now known. There are many people who manufacture different kinds of hemoglobin, which they have in their red cells, molecules differing from those manufactured by the ordinary run-of-the-mill human beings; and often it is disadvantageous to manufacture an abnormal hemoglobin.

We understand some of these diseases. I like the ferrihemoglobinemias especially, because they are understood completely. In the hemoglobin molecule the iron atom, which combines with oxygen, is in the bivalent state, ferrous iron. Ordinary ferrous compounds are easily oxidized to the ferric state. But hemoglobin does not oxidize easily to ferrihemoglobin. The reason is that in the 58th position of the 141 amino-acid residues that make up the alpha chain, or in the 63rd position of the 145 amino-acid residues that make up the beta chain in the hemoglobin molecule, there is ordinarily a residue of histidine, which has a five membered ring with two nitrogen atoms. The imidazole ring of histidine is basic and picks up a proton, which gives it a positive electric charge. This positively-charged group, near the iron atom, keeps it from going from charge plus two to plus three, just by the electrostatic repulsion of the extra positive charge.

If you have a molecular disease in which the 58th position of the alpha chain or the 63rd position of the beta chain is occupied by tyrosine instead of histidine—closely similar, but neutral, not positively charged—then the iron atom oxidizes to the ferric state, and the person suffers from ferrihemoglobinemia. This involves only the alpha chain or the beta chain; hence his hemoglobin carries only half as much oxygen as an ordinary person, and he suffers somewhat from the defect. He may have his tissues damaged under some conditions by anoxia.

As time goes by we shall understand these molecular diseases more and more; and be able, for many of them, to develop specific drugs, therapeutic chemical agents that will control them. This is already going on. We have the treatment of diabetes by injecting insulin, and of phenylketonuria by a low-phenylalanine diet.

There is the possibility, as Dr. Medawar said, of the consequent deterioration of the pool of human germ plasm. What are we going to do about it?

I think that what we should do is to keep the heterozygotes in these serious diseases from marrying one another. If two heterozygotes marry, a quarter of the children would inherit the abnormal gene from both the father and the mother, and would have physical or mental defects leading to great suffering.

I have advocated that there be tattooed on the forehead of each boy or girl symbols indicating the seriously defective genes that he or she carries so that those carrying the same seriously defective gene would refrain from falling in love with one another.

But it would not be enough for the heterozygotes to refrain from marrying one another. There are some thousands of sickle cell anemia patients born every year. If no pairs of heterozygotes were to marry, there would

be no more children born with the disease; but if they married normals, and had the same number of children as other people have, the gene would continue on with the same incidence as at present. I think that not only should the known heterozygotes refrain from marrying one another, but also if one marries a normal person, he should have the obligation to have a decreased number of children. In that way the gene would die out gradually, or be at least decreased to an incidence determined by new mutations, without the suffering involved in the birth of the seriously defective homozygotes.

The sources of happiness in this world are not so great that we should neglect any of them. Understanding the world is worthwhile. My former associate Emil Zuckerkandl, now in Montpellier, worked on the hemoglobin of animals, including the horse and the gorilla. He found that in the beta chain of the human and the beta chain of the horse, for example, 20 of the 146 amino acids are different; but with human and gorilla, only one is different. It is the same amount of difference, just one amino acid residue, as between ordinary humans and sickle cell anemia patients, who manufacture sickle-cell-anemia hemoglobin.

The difference of twenty between horse and human corresponds to one evolutionarily effective mutation every four million years.

Emil Smith and Emil Margoliash have studied cytochrome C, an iron-containing enzyme present in cells, and have found that of the 105 residues only six are different, not twenty. And when you go farther down, human and tuna fish, only 15 are different; for human and yeast, only 40 are different, out of the 105. In 65 positions, the choice from among the twenty amino acids that might be present in each position is the same for yeast and human beings. This shows how closely similar we are. We are close cousins even of bread yeast.

Why is hemoglobin changing more rapidly than cytochrome C? I think the answer is that hemoglobin is a young protein. It has, no doubt, old parentage but it is young; because only when, about 600 million years ago, animals became big enough to require an oxygen-carrying protein in their blood to carry oxygen back and forth, only then did a gene, which was a result of gene duplication, start manufacturing hemoglobin molecules. But already yeast cells and other cells had been making use of cytochrome C for a very long time, for a billion years. The process of evolutionary selection of cytochrome C was nearly ended when that for hemoglobin began.

Emil Zuckerkandl said to me one day that the expulsion from the Garden of Eden was a molecular disease that our ancestors interpreted as evolution. We require nine amino acids in our food, the nine essential amino acids. We can manufacture the other eleven. The red bread mold can synthesize them all, and all the vitamins, too, except biotin. We have lost some of the abilities that the red bread mold has. Every vitamin, every essential amino acid, every essential nutrilitite represents a molecular disease that our ancestors learned to control by diet; and we continue to live because we treat these molecular diseases by a proper diet.

There is an advantage to suffering from a molecular disease, if you know how to treat it. The advantage is that you have gotten rid of some bodily machinery. You are lighter in weight. You don't have to breathe so hard to provide extra energy to manufacture these vitamins and essential amino acids. You get them more easily in your food than by synthesizing them in your body.

It may well be that we could develop a better sort of human being if we found mutants who had lost some other abilities; perhaps all twenty amino acid residues ought to be provided in the diet, so that we would not have to manufacture any of them. I don't really look forward to it—I'm not sure it would be much fun to give up all the bodily functions. I remember that when my friend J. D. Bernal, in 1928, published a book called "The World, the Flesh, and the Devil," he foresaw the time when a human being might be only a giant brain, with minuscule appendages attached, and with a machine providing the nutrient medium. That would be going too far, I think!

I believe that we should be paying more attention to the natural vital substances, the vitamins and essential amino acids.

The principal cause of suffering in the United States now is mental disease; half of the hospital beds are occupied by mental patients, and 54 percent of the mental patients in the California State hospitals are diagnosed as schizophrenic. Why don't we do more about mental disease, about schizophrenia?

We know that a number of the vitamins are related to mental disease. There have been millions of psychotics living within this century who were psychotic just because they had pellagra, and who were cured when they were given a few milligrams of niacin per day.

We know that mental symptoms are associated with a number of other avitaminoses; and there are reports in the literature that using large amounts of vitamins helps some mental patients.

I published a paper last April, entitled "Orthomolecular Psychiatry," in which I said that it may well be that, as Dr. Abram Hoffer and Dr. Humphry Osmond have claimed, giving schizophrenic patients three grams a day, or more, of niacin or niacinamide leads to an increase in the number in whom the disease is controlled.

There are also some published reports that large doses of ascorbic acid (vitamin C), cyanocobalamin (B₁₂), pyridoxine (B₆), and some other vitamins have been found to be of value in controlling mental disease in some patients.

A large intake of vitamin C, one gram a day, or more, has been reported to be of value also in accelerating wound healing and recovery from infection, including the common cold. These reports have been rejected by most medical authorities, who have contended that the usually recommended daily intake, about fifty milligrams, is enough for every person. It is my opinion that we do not know what the optimal daily amount of vitamin C is. I think that for most human beings it may lie between one gram and five grams per

day, far more than the usually recommended fifty milligrams per day; and, moreover, as Professor Roger J. Williams has emphasized, that there may be large differences in the needs of different human beings.

We should know what the optimal daily amounts of the various vitamins are. This is a medical problem that should be attacked and solved.

Starvation and malnutrition present a medical problem as well as a social problem.

And crime is also in part a medical problem. I read last week that a man who had killed a woman was acquitted in Melbourne, Australia, because microscopic studies of his cells showed that he had 47 chromosomes, an extra Y chromosome. It has been found, in several countries, that one to five percent of male criminals over six feet tall have this abnormal chromosomal constitution, an extra Y chromosome. They are criminals because—with little doubt—of this abnormality. But aren't most criminals criminals because of either a genetic abnormality or the faults of society?

In the United States we are following the wrong course. I think that the world as a whole is improving, but that we have been going in the wrong direction. We are making the rich richer and the poor poorer. Over the last ten years, the average income from investments has nearly doubled in rate. This means that the increase in the gross national product goes largely to benefit the wealthy, and to give them more and more of a stranglehold on the economy of the country, and of the world—rather than going to relieve the suffering of the poor.

Twenty percent of the Negroes in the United States have an average annual income of only \$250 a year. This very small income leads to illness and suffering.

The governments of the world show their immorality by wasting ten percent of the world's production on militarism. Doctors should be opposed to war. More than 30,000 Americans have been killed in Viet Nam, and several hundred thousand injured. Last year we were bombing Viet Nam at the rate of 800,000 tons of TNT per year. During the second world war, bombing was effective in killing people at the rate of 4/10's of a death per ton of TNT. The population density of Viet Nam is about the same as in Germany, which permits the estimate that we were killing about 300,000 Vietnamese a year. This is a medical problem; the duty of physicians is to help keep people alive.

You know, there was a time when the religious leaders were the scientists and physicians; and in some societies, they still are—the shaman, the witch doctor. Then a sort of specialization came in. It shocks me that the religious leaders of our country have, for the most part, supported the war in Viet Nam. And, of course, most, although not all, of the physicians have supported this war.

I remember when my wife and I went to Mexico City in 1949 to attend the Western Hemisphere Conference on World Peace. A couple of thousand people were there from all of Latin America; and we were astonished and pleased to find that many of the leaders in the fight against war in these

Latin American countries were physicians. There were 110 participants from the United States; as I remember, there wasn't a physician among them.

Physicians, who are interested in the welfare of individual human beings, should be working to keep people from being killed and injured in war.

I said that our government is not alone in being immoral. I think that it now leads the world, because of the war in Viet Nam; but there are others. We have seen an example of immorality in Czechoslovakia—the action of the government of the U.S.S.R.

Leo Huberman recently wrote in the *Monthly Review*: "The Czech people wanted to democratize the system, the communist system there. Did it need democratization? In Czechoslovakia, as in the Soviet Union, and all the people's democracies, the record was indeed frightful: Bureaucracy and over-centralization carried to extreme lengths; appalling violations of civil liberties; wholesale arrests; torture and false confessions; deprivation of freedom and life for large numbers of people; no really effective participation by the masses in deciding who was to govern them and how they were to be governed; deception, hypocrisy and lies, the characteristic behavior of the privileged ruling groups."

It sounds in part like the United States, the lies at the time of the Bay of Pigs. We don't have many political prisoners—perhaps Dr. Spock will be one soon—but we are pretty free of that at the present time.

I shall make another comparison. We, the United States, prevented a scheduled democratic election from being held under international auspices in Viet Nam in 1955; and hundreds of thousands of people have died as a result. Only 37 people were reported to have been killed at the time of the invasion of Czechoslovakia. Both of these acts were immoral; but they differ in scale.

I hope that the medical profession during the coming years will follow a course that will lead to greater morality in the world.

I think that doctors ought to be well paid. They work hard: too hard. I would like to see twice as many physicians, three times as many physicians, with a guaranteed income, which would enable them to lead good lives; and with reasonable working conditions, so that they would have time to develop themselves and to enjoy this wonderful world in which we live.

I hope that you young people, you young men and women in this fine new medical school, will have a wonderful time during the coming years. I think that you will, because medicine is now in a wonderful state of development, and there are greater possibilities for the future than there ever have been before. I hope that you will follow the lead of Dr. Thomas Addis, and of Dr. Benjamin Spock, who has become a leader in the fight for peace in the world, and of Dr. George James, with his deep concern for the welfare of humanity, even the underprivileged part of humanity; and that you will devote part of your effort to changing your profession, changing it into the practice of medicine in a rational world.

The Use of Valve Homografts in Cardiac Surgery

PAUL MARCHAND, M.D., Ch.M., F.R.C.S.*†

Howard Lilienthal died on April 30th, 1946 at the age of 85 after a lifetime of service to this hospital. His career which started at Harvard Medical School in 1887 spanned the two eras, "before Lister and after Lister." His generation had the exciting privilege of practising surgery as it emerged from the dreadful handicaps of pain and of sepsis. Lilienthal, a bold and resourceful man, was destined to succeed and indeed he flourished in an epoch of surgical dexterity, but the chest and, in particular, the heart continued to present formidable problems. In Lilienthal's lifetime, Bilioth said, "Let no man who wishes to retain the respect of his medical brethren dare to operate upon the human heart," and Lord Moynihan believed that his generation "had reached the limits set by nature to all surgery." These great men, secure in their eminence and surrounded by the political and social stability of their age, failed to foresee that progress in other fields would eventually make cardiac surgery possible. But others had broader vision. In 1925 Lilienthal (1) expressed his belief that the thoracic organs, including the heart and great vessels, merited special study and that thoracic surgery would evolve as a speciality "in spite of violent protest from the old practitioners." His prediction was that: "In the heart and great vessels brilliant things may be expected in future operations in human subjects.... With medicine and surgery working for the same object without rivalry and without envy, we may look forward to the future of this great new speciality with confidence and hope." Lilienthal's technical achievements were ahead of his time: A successful lobectomy in 1914 and an esophagectomy in 1921! This was the direct path to the heart and though he died shortly before the feats of Blalock, Brock, Bailey, and Gibbon, he must, in old age, have known that his life had helped to make direct cardiac surgery possible. The 22 years since his death have justified his faith. He would surely have delighted to be part of them although I fear that, with his mechanical gifts, he would have opted for prostheses rather than for homografts for the replacement of heart valves.

Transplantation of homologous valves were first performed by Murray (2). He placed them in the descending aorta of animals and of three patients. With open heart surgery it became possible to insert them in the subcoronary position. The pioneers were Ross (3), Duran and Gunning (4) and Barratt-Boyes (5). Here in North America, blessed with technical and engineering skills and to us foreigners, possessed of seemingly limitless funds, surgical efforts were directed mainly towards prosthetic valve replacements. My experience with prosthetic aortic valves started in August 1963 and

* Head of the Department of Cardio-Pulmonary Surgery, Johannesburg Hospital and University of the Witwatersrand, Johannesburg, South Africa.

† This paper was presented as the Howard Lilienthal Lecture on November 16, 1968 at The Mount Sinai Hospital, New York, N. Y.

is confined to the Starr-Edwards valve. I turned to homografts largely because of my abhorrence at the thought of life dependent upon a structure of steel and plastic. My first homograft operation was performed in September 1964. As experience lengthened I used the natural aortic valve increasingly and extended its application to the pulmonary (6, 7) and mitral valves. Homograft introduction is a difficult operation and those who aspire to advocate its general use must demonstrate that homografts are durable and subject to few long-term complications.

Material

From September 1964 to October 1967 I replaced 55 aortic valves, 6 pulmonary valves and 6 mitral valves with aortic homografts. From July 1963 to October 1967, 76 Starr-Edwards replacements of the aortic valve were performed.

Preparation of Homografts

Grafts are prepared in standard fashion for all three purposes. They are collected unsterile. Any valve which looks healthy and can be prepared within 36 hours of death is acceptable. The ascending aorta is removed together with the anterior mitral leaflet. Muscle, adventitia, and mitral chordae are trimmed leaving a basal fringe consisting of the mitral leaflet, 2 mm of muscular septum and parts of the right and left trigones. The valve is graded by measuring the internal circumference of the aortic 'ring.' It is hydrostatically distended to test for competency. It is sterilized by six hours' exposure to 15% ethylene oxide gas. The valve is freeze dried and sealed in an evacuated container. Grafts have been used after a year of storage. When required, the seal is broken and the container filled with an antibiotic-saline solution containing streptomycin, penicillin, and amphotericin B. It reconstitutes within 30 minutes.

Aortic Valve Homografts

METHOD OF INTRODUCTION

The host cusps are excised and the bed freed of calcium. The internal circumference of the host's aortic 'ring' is measured so that a matching homograft can be selected. This is finally prepared by excising the aortic walls of the left and right coronary sinuses leaving a mm fringe. The noncoronary aortic wall is retained and the anterior mitral leaflet is removed.

The graft is introduced by suturing the basal ring beneath the left and right coronary cusps to the corresponding subvalvular area of the host with 12-15 interrupted sutures. It is eased down along these sutures and the commissural pillars are inverted into the left ventricle. The sutures are then tied. The basal ring suturing is then completed by sewing its portion beneath the noncoronary cusp to the corresponding cusp remnant of the host. The

commissural pillars are everted and the fringes of the right and left cusps are sewn to the host's fringes with continuous or interrupted sutures.

When a bicuspid host valve is present the graft's commissural pillars are freely sewn to the aortic wall. An important point of technique is to produce deep cusps by slinging the commissural pillars as high as possible. I attempt to hitch the homograft commissures higher than the originals. The free edge of the noncoronary aortic wall is sewn across the aorta to bolster the lower end of the aortotomy. To avoid bunching the noncoronary cusp it may be necessary to close the lower end of the aortotomy with a diamond-shaped dacron gusset. Introduction is more laborious and time-consuming than for a prosthesis. By-pass times vary from 70–100 minutes.

Homografts in the Aortic Position

The ages of the 55 patients ranged from 15 to 62. Thirty-seven were males and 18 females. Etiology was rheumatic in 35, calcific in 11, post-bacterial endocarditis in 4, traumatic in 2, congenital in 1 and associated with Marfan's disease in 1. Fourteen cases were stenotic, 22 incompetent and 19 were mixed lesions. Cases were either in functional grade III or IV (A.H.A. Classification). Simultaneous mitral valve surgery was performed in 19. All patients have been followed more than a year and have been recently assessed by two independent cardiologists. Twelve patients have had post-operative catheter studies.

MORTALITY

Seven patients died whilst in hospital. This mortality of 12.5% compares with 14 deaths amongst the Starr-Edwards replacements (18%). Of the 48 survivors 3 (6%) have died since discharge from hospital one from infective endocarditis, one from an arrhythmia which had been present preoperatively and one from intestinal obstruction. The late Starr-Edwards deaths number 12 (20%). (Table I)

Complications

The complications of Starr-Edwards replacement and homografts are compared in Table II. With homografts there have been no peripheral emboli and anticoagulants have not been used. No patient experienced sudden severe aortic incompetence due to cusp rupture unless complicated by bacterial endocarditis.

INFECTIVE ENDOCARDITIS

Three of the 6 cases occurred in hospital (two deaths) and the infection can probably be ascribed to error in aseptic discipline, either at surgery, in sterilizing the graft, or because of ill-conceived, overintensive antibiotic regime. Two were fungal infections (both died) and in consequence we are now less aggressive with postoperative antibiotics. Three cases of infective

TABLE I

Comparison between the Late Deaths of Starr-Edwards and Homograft Replacements of the Aortic Valve

The follow-up period is a year longer for the Starr-Edwards patient.

	STARR-ED.	HOMOGRAFTS
Emboli	5	0
S. B. E.	5	1
A.I. Ball variance Ring leak.	2	0
Arrhythmia	0	1
Intestinal Obstruction.	0	1
Total	12 (20%)	3 (6%)

LATE DEATHS

TABLE II

Comparison of the Serious Late Complications

These have occurred in 34% of the prosthetic cases and 15% of the homografts.

	STARR-ED.	HOMOGRAFTS
Number	62	48
Emboli	7 (11%)	0
S. B. E.	6 (10%)	3 (6.5%)
Severe A.I.	2 (3%)	3 (6.5%)
Anaemia	6 (10%)	0
Calcification	0	1 (2%)
Follow-Up	1-5yrs.	1-4yrs.

SERIOUS LATE COMPLICATIONS

endocarditis (one death) occurred more than 16 months after introduction. Three of the 6 cases were cured. All three deaths were associated with fungal infection with *aspergillus niger*. With prostheses there has been one cure in 7 cases (14%).

AORTIC INCOMPETENCE

Assessment of aortic incompetence has been based upon the blood pressure and auscultation alone in 36 cases with the addition of aortography in 12 patients (Table III). Thirteen (27%) have no incompetence. In 24 (50%), incompetence is haemodynamically insignificant, the murmur is faint, the pulse pressure normal and indeed in 4 patients the only evidence is a regurgitant whiff seen angiographically. In 8 cases (17%) pulse pressures are not unduly wide but murmurs are clear. There are 2 cases (4%) with significant incompetence and one patient required removal of the homograft and replacement with a prosthesis. This patient had Marfan's disease.

TABLE III

*Comparison between the Incidence of Aortic Incompetence
in the Two Groups*

Major degrees of incompetence are not dissimilar in incidence.

	Starr-Edwards	Homograft
Competent	47 (85%)	13 (27%)
Grade 1.	0	24 (52%)
Grade 2.	4 (6 %)	8 (15%)
Grade 3.	4 (6 %)	2 (4 %)
Grade 4.	2 (3 %)	1 (2 %)

AORTIC INCOMPETENCE

DURABILITY

It is extraordinary that incompetence has not been progressive except with bacterial endocarditis. The first patient's graft had been mistakenly immersed in alcohol and this is the only one which has calcified. All survivors are symptomatically improved.

Necropsies were refused on the two patients who died with uninfected valves so that we have not had the opportunity of studying the cusps of an uninfected long-term survivor. The reports of Hudson (8) and of Smith (9) indicate that normally grafts are well accepted by the host and that despite the absence of revascularisation, the cusps retain their structure and flexibility. Both authors strike a note of caution with regard to late cusp rupture, calcification and progressive thickening at the bases of the cusps.

HAEMODYNAMIC STUDIES

Postoperative catheterisations have shown excellent haemodynamic function. The maximum systolic gradient across the valve has been 10 mm of mercury. Two postoperative catheter studies were repeated 14 months apart with identical results proving that progressive deterioration has not occurred.

Conclusions

Currently it is exceptional if more than a faint diastolic murmur is present. This improvement is ascribed to technical experience and to fairly accurate matching of the homograft to the host's aorta. It is upon the score of incompetence, which is linked with meticulous and prolonged surgery, that homografts are unfavourably compared with prostheses. Although no cusp has ruptured in four years this has occurred in both Ross' and Barratt-Boyes' far more extensive experience. It must be remembered that dislocation of the plastic Starr-Edwards ball does occur. This has happened once in our series and twice in our small experience of double valve replacements not included in this survey. The new metal ball may prevent this happening in

the future. Also, incomplete adherence of the prosthetic ring to the host aorta is not uncommon with prosthetic replacements so that a prosthesis is no absolute guarantee of competence (Table III).

As I see it the main disadvantages are that the surgical technique is laborious and that graft sterilisation is not completely certain.

The clear advantages of homografts over prostheses are:

1. No postoperative emboli
2. No haemolysis
3. A 50% cure rate of S.B.E.

Acknowledgments

The experimental background of this work was done with the assistance of the C.S.I.R. (South Africa) and the Johannesburg City Council. I wish to thank Drs. J. Barlow, I.W.P. Obel, and L. du Plessis for their cooperation in the assessment and management of the cases here reported.

References

1. Lilienthal, H.: Thoracic Surgery as a Speciality, *Ann Surg* 81:191, 1925.
2. Murray, G.: Homologous Aortic Valve Segment Transplants as Surgical Treatment for Aortic and Mitral Insufficiency, *Angiology* 7:466, 1956.
3. Ross, D. N.: Homograft Replacement of the Aortic Valve, *Lancet* 2:487, 1962.
4. Duran, C. G., and Gunning, A. J.: A Method for Placing a Total Homologous Aortic Valve in the Subcoronary Position, *Lancet* 2:488, 1962.
5. Barratt-Boyes, B. G.: Homograft Aortic Valve Replacement in Aortic Incompetence and Stenosis, *Thorax* 19:131, 1964.
6. Fuller, D. N., Marchand, P., Zion, M. M., and Zwi, S.: Homograft Replacement of the Pulmonary Valve, *Thorax* 21:337, 1966.
7. Marchand, P.: The Use of a Cusp-bearing Homograft Patch to the Outflow Tract and Pulmonary Artery in Fallot's Tetralogy, *Thorax* 22:497, 1967.
8. Hudson, R. E. B.: Pathology of the Human Aortic Homograft, *Brit Heart J* 28:291, 1966.
9. Smith, J. C.: The Pathology of Human Aortic Valve Homografts, *Thorax* 22:114, 1967.

The Pulmonary Valve

The surgical experience of correction for Fallot's tetralogy has shown that failure is usually due to incomplete relief of the pulmonary obstruction (10, 11). Lillehei and his co-workers therefore introduced outflow tract patching. They also emphasized that it is sometimes necessary to divide the ring and occasionally to extend the patch to the bifurcation of the pulmonary artery. Our group described the use of a homograft pulmonary valve in a patient with massive pulmonary incompetence following pulmonary valvotomy (6). Since then we have replaced one or more cusps of the pulmonary valve in 5 additional cases. Preparation of the graft has been fully documented (7) (Fig. 1). We have used 1, 2 and 3 cusp replacements to enlarge the outflow tract of the right ventricle and pulmonary trunk so avoiding serious pulmonary incompetence.

RESULTS OF SURGERY

All survivors have been seen recently. They are well and leading normal lives. Catheter slides reveal no gradients across the valves and pulmonary angiograms have shown little or no pulmonary incompetence.

DISCUSSION

Kirklin, Payne, Theye, and DuShane (13) believe it unlikely that a patient will survive operation for Fallot's tetralogy if a residual right ventricular pressure greater than 50% of the aortic pressure remains. Virtually all gradients have been overcome by the grafting technique described.

With good myocardial function pulmonary incompetence can be tolerated well. On the other hand Bender, et al (18) have demonstrated that sudden pulmonary incompetence results in acute depression of effective right ventricular function. The very existence of the pulmonary valve makes it inconceivable that incompetence is unimportant.

The valve ring is always small in pulmonary valve stenosis. The circumference of the aortic and pulmonary valve rings have been measured in normal hearts and in specimens of Fallot's tetralogy. The average ratio between the aorta and pulmonary artery in normal hearts is 82% whereas that in Fallot's tetralogy is 160%. Ideally every case of pulmonary valvular stenosis should have the ring enlarged to a circumference of at least 7-9 cm. This should be possible using one, two or three cusp homografts.

The Mitral Valve

The long-term results of prosthetic mitral valve replacement are often spoilt by emboli (Fig. 2). The absence of emboli with homografts in the aortic and pulmonary positions encouraged us to use them for mitral replacement.

Only homografts with a circumference greater than 9 cm are suitable. A strip of thin Teflon about 10 cm \times 2 cm, is wrapped around the base of the graft and is tailored as shown in Figs. 3b, c, d, and e. Tailoring is aimed at preserving and supporting the sinuses of Valsalva.

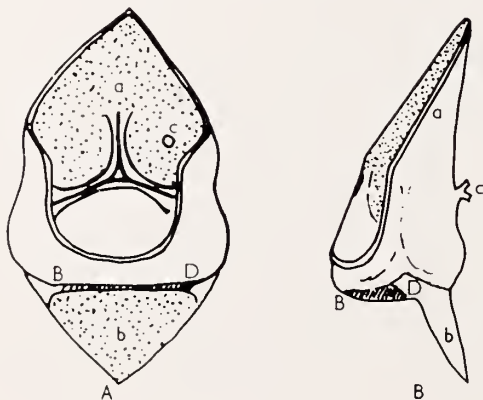


FIG. 1. Diagram of the homograft. The stippled areas are the parts of the aorta and mitral leaflet used to enlarge the pulmonary artery and right ventricular outflow respectively. The cross-hatched line (B-D) represents the muscular remnant of the ventricular septum. (A) Viewed from behind with aortic wall excised from noncoronary cusp. (B) Viewed from the side; a, tongue of aorta; b, mitral leaflet; c, left coronary artery.

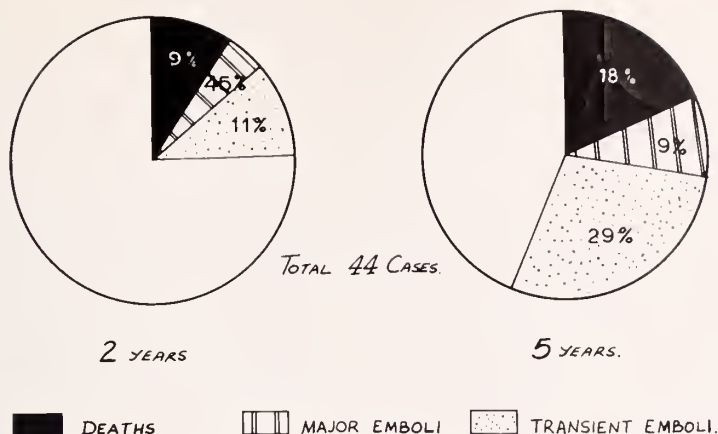
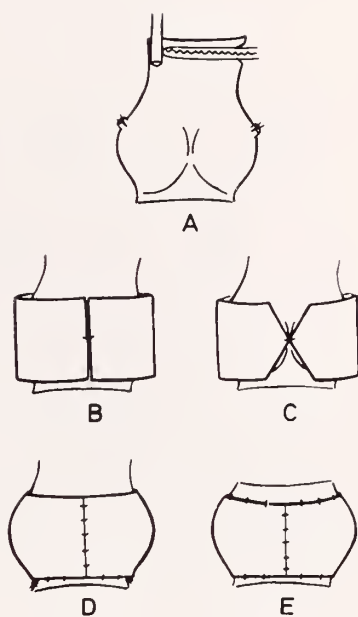


FIG. 2. Incidence of emboli in 44 patients who survived prosthetic mitral valve replacement performed 3 to 5 years ago. Comparison between the incidence in the same group after an interval of 3 years.

FIG. 3. Technique of tailoring the Teflon jacket to the homograft.

- Aortic homograft tensely distended with saline.
- Teflon strip wrapped around valve bearing area.
- Method of cutting the Teflon over positions of each of the 3 commissures.
- Sewing the Teflon so that the strip hugs the contours of the sinuses of Valsalva.
- Completed preparation with fringes projecting beyond the Teflon at each end.



The method of insertion resembles that reported by Kay (19). Under cardiopulmonary by-pass the anterior mitral leaflet is excised leaving a centimeter fringe attached to its annulus. If possible the posterior leaflet is preserved with chordal and muscle attachments (Figs. 4a and b). The aortic end of the graft is sutured to the edges of the mitral curtain remnant. When anastomosis is complete the left ventricle is filled with blood by releasing the aortic clamp and distorting the aortic cusps so as to close the homograft leaflets and distend the graft into the atrium. Sutures are then placed in the

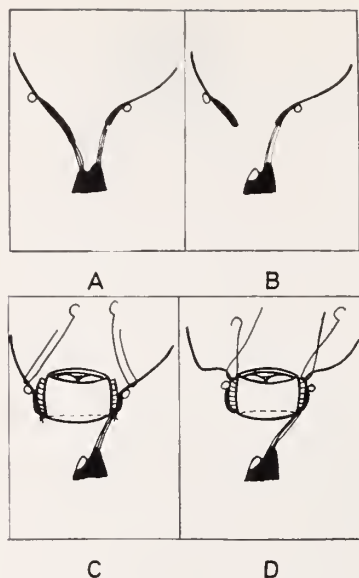


FIG. 4. Method of introduction of tube graft.
 a) Diagram of mitral mechanism (anterior leaflet is the longer)
 b) Excision of portion of anterior leaflet, chordae, and head of papillary muscle.
 c) Basal suture line completed. Tube graft distended into left atrium. The approximating atrial stitches are shown.
 d) Atrial wall sutured to base of graft. If calcification is total the basal suture is to the valve ring.

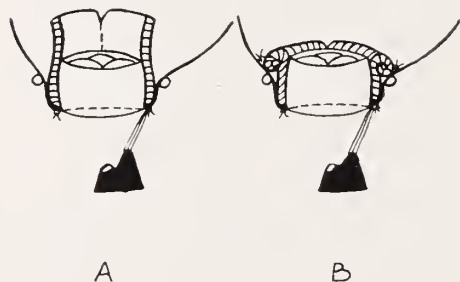


FIG. 5. Present modification technique. The Teflon strip is wider than shown in Fig. 4 and it projects beyond the base of the inverted graft. The Teflon skirt is folded down to form a basal ring filling the angle between the atrial wall, annulus, and side of the tubular graft. This avoids distortion of the atrium.

atrial wall to approximate it to the base of the graft (Figs. 4c and d). Unfortunately these sutures, particularly posteriorly, may distort the cusps and cause incompetence. The technique has since been modified by using a wider strip of Teflon to form a 2 cm skirt projecting beyond the graft. This is split longitudinally to the base of the valve with three equidistant incisions. When the graft is distended into the atrium the Teflon skirt is rolled down to form a basal ring filling the angle between the graft and the annulus (Fig. 5).

Results

Six patients were operated upon more than a year ago. Two died in hospital and in one case mitral incompetence was so severe that it was replaced with a prosthesis the same day.

The 3 survivors are well but 2 have residual mitral incompetence. There have been no emboli and anticoagulants have not been used.

All 3 patients have been catheterised. Small early diastolic gradients are present. Assessment of the degree of regurgitation has been difficult. The first patient has a competent valve, nevertheless an unduly prominent "V"

wave is present which is attributed to the small left atrium. It is likely that the similarly small left atria of the second and third patients are responsible for the large "V" wave of the left atrial pressures although both have moderate incompetence.

Discussion

These patients confirm that an aortic homograft can fulfill the requirements of a left atrioventricular valve. The large size of the graft required is a limiting factor. Only 14% of all adult grafts have a basal diameter of more than 9 cm. Ionescu et al (20) have overcome this difficulty by using pig heterografts. Lower, et al (21) used homologous pulmonary valves for mitral replacement in dogs and Ross (22) has used autologous pulmonary valves thus demonstrating that the pulmonary valve can withstand left ventricular pressures.

With regard to homografts in the mitral position, we share Starr's reservations (23), only more so, about his latest prosthesis and believe they should be used only where no conservative procedure is possible.

References

10. Lillehei, C. W., Cohen, M., Warden, H. E., and Varco, R. L.: Complete Anatomical Correction of the Tetralogy of Fallot, *Arch Surg* 73:526, 1956.
11. Kirklin, J. W., et al: Applicability of Gibbon-type Pump-oxygenator to Human Intracardiac Surgery: Forty Cases, *Ann Surg* 144:2, 1956.
12. Lillehei, C. W., Morris, M. J., Adams, P., and Anderson, R. C.: Corrective Surgery for Tetralogy of Fallot, *J Thorac Cardiovas Surg* 48:556, 1964.
13. Kirklin, J. W., Payne, W. S., Theye, R. A. and Du Shane, J. W.: Factors Affecting Survival after Open-heart Operation for Tetralogy of Fallot, *Ann Surg* 144:2, 1960.
14. Ellison, R. G., Brown, W. J., Hague, E. E. and Hamilton, W. F.: Physiologic Observations in Experimental Pulmonary Insufficiency, *J Thorac Surg* 30:633, 1955.
15. Fowler, M. D., and Duchesne, E. R.: Effect of Experimental Pulmonary Valvular Insufficiency on the Circulation, *J Thorac Surg* 35:643, 1958.
16. Blount, S. G., McCord, M. C., Mueller, H. and Swan, H.: Isolated Valvular Pulmonic Stenosis—Clinical and Physiologic Responses to Open Valvuloplasty, *Circulation* 10:161, 1954.
17. Price, B. O.: Isolated Incompetence of the Pulmonic Valve, *Circulation* 23:596, 1961.
18. Bender, H. W., et al: Experimental Pulmonic Regurgitation, *J Thorac Cardiovas Surg* 45:451, 1963.
19. Kay, E. B.: Heterotransplantation of the Human Pulmonic Valve to the Calf Pulmonic Area. Discussion of Thoracic Surgery Forum, *J Thorac Cardiovas Surg* 52:870, 1966.
20. Ionescu, M. I., Smith, D. R., and Grimshaw, V. A.: Mitral Valve Replacement with Aortic Heterografts in Humans, *Thorax* 22:305, 1967.
21. Lower, R. R., Stofer, R. C., and Shumway, N. E.: Total Excision of the Mitral Valve and Replacement with the Autologous Pulmonic Valve, *J Thorac Cardiovas Surg* 42:696, 1961.
22. Ross, D. N.: Replacement of the Aortic and Mitral Valves with a Pulmonary Autograft, *Lancet* 2:956, 1967.
23. Starr, A.: Heterotransplantation of the Human Pulmonic Valve to the Calf Pulmonic Area—Discussion of Thoracic Surgery Forum, *J Thorac Cardiovas Surg* 52:872, 1966.

Carpal Tunnel Compression Syndrome

Unusual Case Reports

ANGELA A. RAMIREZ-IRIZARRY, M.D.*, AND
LEON BLUESTONE, M.D., F.A.C.S.†

Median nerve compression within the carpal tunnel was originally reported by Paget in 1865 (1). Hunt in 1909, attributed thenar atrophy to compression of the median nerve beneath the ligament (2), Marine and Fox in 1913 (3) and Moersch in 1838 (4) suggested the possibility of treatment by sectioning the ligament but it was not until 1941 that Waltman first reported the successful treatment of median neuritis by surgical decompression of the nerve (5).

Two compartments are present in the tunnel; i.e., a superficial one (Richet's canal), through which runs the flexor carpi ulnaris tendon and a deeper one, through which pass the median nerve and all of the flexor tendons (6, 7). It is in the latter where flattening and constriction of the nerve can be produced whenever there is impingement upon the limited space. The ulnar nerve also presents a similar situation at the wrist, where the volar carpal ligament on top and the transverse carpal ligament below form a tunnel in which compression neuritis of the nerve can be produced (8). The reported cases of ulnar tunnel compression syndrome, however, are few in comparison.

Case Reports

Case No. 1. J.B. (E.G.H. #1990). A right-handed, 51-year-old male elevator operator, unemployed for six months because of cardiac pathology, was awakened on the night prior to admission by severe pain shooting down his left arm into all his fingers. This was accompanied by inability to fully flex his fingers and by numbness in the thumb, index, and middle fingers. There was also a sensation of a shooting, "electric" pain going from the wrist into all his fingers following forced flexion or extension of the wrist.

The patient held his hand and wrist in a neutral position, with any attempt at either full flexion or extension of the fingers causing severe pain. There was hyperhydrosis and erythema of the entire hand, a positive Tinel sign at the level of the wrist, and positive tourniquet and wrist flexion tests. Thenar atrophy was not present. EMG revealed no electrical evidence of either ulnar nor median nerve involvement.

At surgical exploration, 3 weeks later, a fine sheath, its fibers running mostly transversely, enveloped the ulnar nerve producing a significant constriction. Exploration of the carpal tunnel revealed an accessory palmaris brevis muscle compressing the tunnel in its upper portion. The transverse carpal ligament was thickened and scarred, producing proximal pseudo-neuromatous enlargement of the median nerve and gross edema. Excision of the constricting sheath around the ulnar nerve, transection of the accessory muscle and transection of the transverse carpal ligament were performed. Postoperatively, the patient had marked relief from his previous symptoms (Figs. 1A and 1B).

From the Department of Surgery, Division of Hand Surgery, The Mount Sinai Hospital, Elmhurst Services Unit.

Presented at the Sixth Annual Plastic Surgery Residents Conference, American Society of Plastic and Reconstructive Surgeons, Royal Victoria Hospital, Montreal, Canada, April, 1967.

* Chief Resident in plastic surgery and † Chief, Hand Surgical Service, The Mount Sinai Hospital, Elmhurst Services Division, Elmhurst, New York.

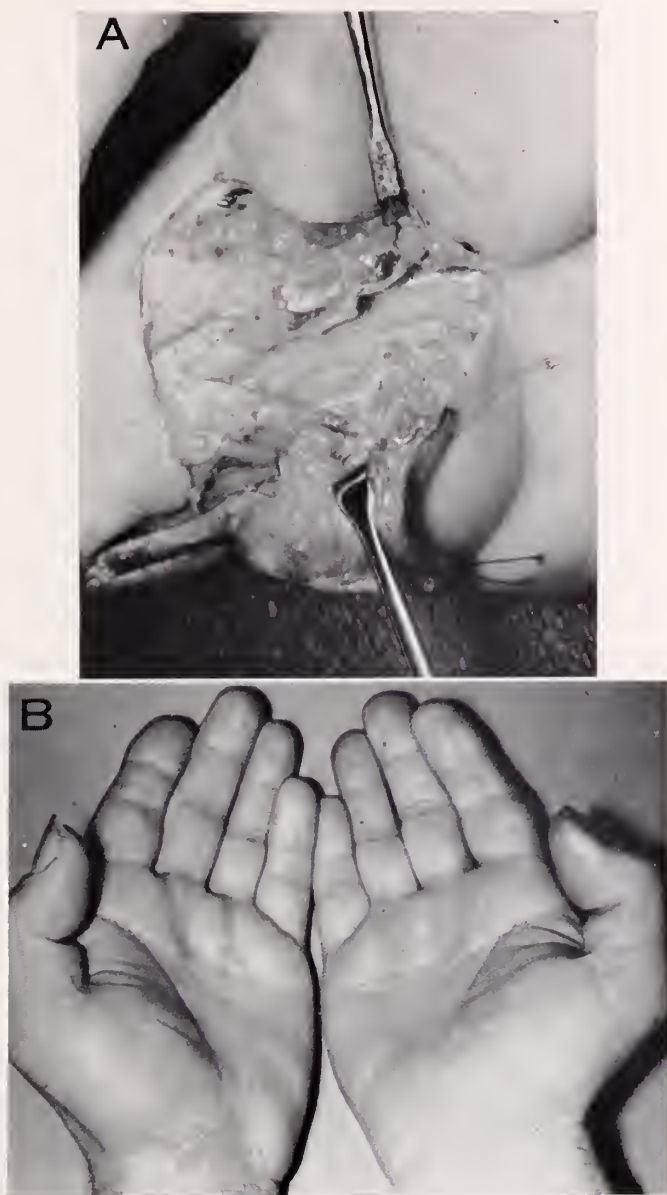


FIG. 1A. Median nerve, following surgical decompression. Nerve is edematous and proximal pseudoneuroma is present. In the proximal limb of the incision, the ulnar nerve can be seen exposed. Sheath formerly compressing nerve has been already transected.

FIG. 1B. Five weeks postoperatively, tenderness of the hand has disappeared and patient is able to achieve full flexion and extension movements with minimal difficulty.



Fig. 2. Two years after injury showing location of burn scar.

COMMENT: The occurrence of median and ulnar nerve compression syndromes in the same hand is rare. The acute occurrence and persistence of symptoms is unusual.

Case No. 2. A.B. (E.G.H. #376108). A right-handed 22-year-old man, an unemployed drug addict, attempted suicide with oral barbiturates on May 9, 1966. After becoming unconscious his right wrist came into contact with an electrical outlet and he sustained deep burns on its volar aspect. During the following three months, clinical evidence developed of sensory median nerve impairment accompanied by a flexion contracture deformity of the hand. EMG studies revealed partial electrical denervation of the nerve at wrist level.

Examination of the hand showed burn scars over the volar aspect of the wrist, with atrophy of the thenar eminence. The thumb was held in a position of flexion-adduction and M-P joint contractures of the remaining four fingers were also present. There was anesthesia along the median nerve distribution.

On surgical exploration, the transverse carpal ligament was found to be thickened. There was gross edema, proximal bulbous enlargement and thickening of the peritendinous synovia. Prompt relief of the sensory symptoms followed the surgical decompression although none of the motor findings changed.

COMMENT: The differential diagnosis of direct involvement of the median nerve by the electrical burn versus secondary involvement by constriction of the carpal tunnel was resolved by exploration.

Case No. 3. R.B. (E.G.H. #276975). A right-handed, 45-year-old white man, an unemployed carpenter, was involved in a motorcycle accident in Cuba, 1½ years prior to admission, sustaining multiple fractures of the right wrist, both arms, and a laceration of his right hand at the base of the thenar eminence. The latter was sutured primarily and for two months following the accident he had a short arm cast on his right arm. Shortly following the original trauma, he noticed that his pinching ability was impaired. This was gradually accompanied by wasting of his right thenar area.

Examination of the right hand revealed a well-healed scar at the base of the thenar eminence. There was inability of the thumb to elevate and completely oppose, as well as atrophy of the thenar musculature. Tinel's sign was negative. There was no sensory impairment. EMG revealed denervation of the median nerve at the wrist level.

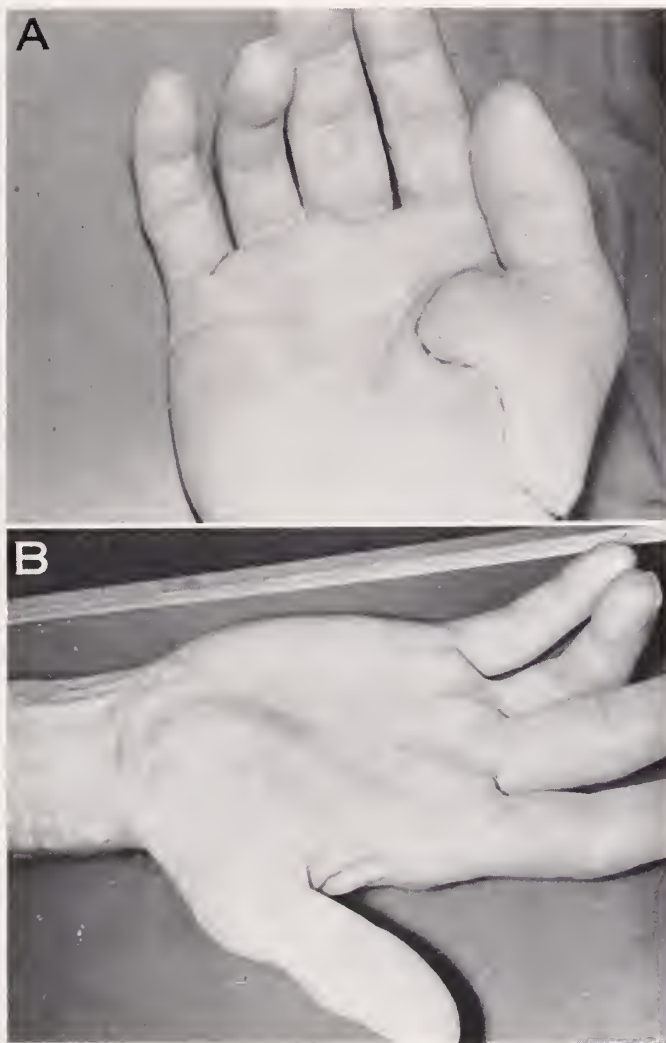


FIG. 3A. Preoperative view, with position of old scar removed. Possibility of laceration of the motor branch of the median nerve immediately considered.

FIG. 3B. At one month postoperative carpal tunnel incision has naturalized well. Thenar atrophy unchanged but thumb function clinically improved.

Impression on admission was that of an old laceration of the motor branch of the median nerve, but carpal tunnel compression of the median nerve could not be ruled out.

On December 22, 1966, under brachial block regional anesthesia, exploration of the median nerve with transection of the transverse carpal ligament was performed for what was grossly found to be a carpal tunnel compression of the nerve with no evidence of actual transection of its motor branch on thorough exploration (Figs. 3A and 3B). After six months follow-up EMG findings suggested return of reinnervation and motor function improved as manifested by better opposition and pinch, and the ability to use the right hand again as the dominant one. Thenar atrophy persisted.

COMMENT: Thenar atrophy and motor dysfunction originally thought to be due to transection of the motor branch of the median nerve was found to be a true carpal tunnel compression at exploration.

Discussion

The causes of carpal tunnel compression include: gouty arthritis or tophi (9), amyloid deposits (10), hypertrophic arthritis at the wrist (11), infection of the radial and ulnar synovial bursa (12), congenital anomalies, ganglia (13, 14), and rheumatoid synovitis. Among the associated systemic diseases which also have been mentioned (15, 16), are the collagen diseases (disseminated LE, polymyositis, dermatomyositis), granulomatous diseases (sarcoidosis), infectious diseases (Tbc.), peripheral vascular disorders (Raynaud's disease), diseases affecting the central nervous system (syphilis, alcoholism), blood disorders (polycythemia vera) and tumors of neural origin (neurofibromatosis). Although most commonly found in postmenopausal women, the syndrome has been frequently reported in pregnancy. The syndrome may occur following trauma of all kinds, including lacerations, fractures, burns, and contusions. It may be masked by other injuries or diseases. It must be considered in all cases that present with a history of sensory disturbance corresponding to the nerve distribution in the hand or with thenar atrophy or weakness. EMG changes may or may not be present, but are fairly diagnostic when present.

References

1. Paget, J.: *Lectures on Surgical Pathology*, Philadelphia, Lindsay and Blakiston, 1965.
2. Hunt, J. R.: Neural Atrophy of Muscles of Hand, without Sensory Disturbances: Further Study of Compression Neuritis of Thenar Branch of Median Nerve and Deep Palmar Branch of Ulnar Nerve, *Rev Neurol and Psychiat* 12:137-48, 1914.
3. Marie, P. and Foix: Atrophie isolée de l'éminence thénar d'origine néuritique. Rôle du ligament annulaire antérieur du carpe dans la pathogénie de la lésion, *Rev Neurol* 26:647-49, 1913.
4. Moersch, F. P.: Median Thenar Neuritis, *Proc Staff Meet Mayo Clin* 12:220-22, 1938.
5. Woltman, H. W.: Neuritis Associated with Acromegaly, *Arch Neurol and Psychiat* 45: 680-82, 1941.
6. Tanzer, R. C.: The Carpal Tunnel Syndrome. A Clinical and Anatomical Study, *J Bone and Joint Surg* 41-A:626-34, 1959.
7. Fernández-Sabaté, A.: Carpal Tunnel Syndrome, *Med Clin* 45:243, 1965.
8. Dupont, C., Cloutier, G. E., Prévost, Y., and Dion, M. A.: Ulnar Tunnel Syndrome at the Wrist: Report of Four Cases of Ulnar Nerve Compression at the Wrist, *J Bone and Joint Surg* 47-A:757-61, 1965.

9. Eard, L. E., Bickel, W. H., and Corbin, K. B.: Median Neuritis (Carpal Tunnel Syndrome) Caused by Gouty Tophi, *JAMA* 167:844-46, 1958.
10. Rubio, F.: Carpal Tunnel Syndrome, (Correspondence) *JAMA* 172: 733, 1960.
11. Quenlan, A. G.: Carpal Tunnel Syndrome Presenting as a Complete Median Nerve Palsy with Trophic Changes, *Brit Med J* 1:32, 1967.
12. Leditschke, J. F.: Acute Carpal Tunnel Syndrome, *Australian and New Zealand J Surg* 34:298-300, 1965.
13. Trevaskis, A. E., Tilly, D., Marks, K. M., and Heffernan, A. H.: Loss of Nerve Function in the Hand Caused by Ganglions, *Plastic and Reconst Surg* 39(1):97-100, 1967.
14. Brooks, D. M.: Nerve Compression by Simple Ganglia: Review of 13 Collected Cases, *J Bone and Joint Surg* 34-B:391-400, 1952.
15. Grossman, L. A., Kaplan, A. J., Ownby, F. D., and Grossman, M.: Carpal Tunnel Syndrome—Initial Manifestation of Systemic Disease, *JAMA* 176:259-61, 1961.
16. Yannaguchi, D. M., Lipscomb, P. R. and Soule, E. H.: Carpal Tunnel Syndrome, *Minnesota Med* 48:22-23, 1965.

Received for publication October 7, 1968

Pancreatic Ascites

Case Report: Ascitic Fluid Lipase Utilized for Diagnosis

ROBERT B. WAGNER, M.D., AND STEPHEN H. TOLINS, M.D.

Ascites in an alcoholic is not always secondary to cirrhosis. Infrequently massive ascites may be secondary to a pancreatic pseudocyst. Since the original report by Smith in 1953, only ten cases have been published (2-8). Examination of the ascitic fluid may be diagnostic of pancreatic ascites. Young alcoholics with ascites should be examined for pseudocysts with particular suspicion, especially when pleural effusions are also present. Relief of pancreatic ascites may be rapidly obtained with proper surgical intervention.

The following case report and a comprehensive review of the eleven previously reported cases of ascites associated with pancreatic pseudocysts suggest a readily recognizable clinical and laboratory picture. This tabulation suggests, too, that surgical intervention is mandatory.

Case Report

A 29-year-old Negro man (L.K.T. # 111 28 4283) was admitted to the Bronx Veterans Administration Hospital on July 12, 1967 with complaints of abdominal pain, weakness, vomiting, and swelling of his legs of three months' duration. Alcoholic intake had been heavy throughout the preceding seven years. The pain was dull, epigastric, occasionally radiating into the back. He vomited intermittently and noted a 20-pound weight loss. He denied melena, hematemesis, or jaundice. His past history included rheumatic fever at age 17. The review of systems was noncontributory.

Positive physical findings included a Grade $\frac{3}{4}$ mitral systolic murmur and a Grade $\frac{2}{4}$ diastolic mitral murmur with an opening snap. The abdomen was soft with the liver edge palpable two fingerbreadths below the costal margin. No ascites was noted at this time. A Grade 2 pitting edema of the ankles was present. An admission chest film was negative. Serum amylase and lipase levels were not elevated.

The abdominal complaints persisted with frequent episodes of severe pain, and the gradual development of massive ascites. A chest film taken a month after admission showed bilateral pleural effusions. A barium meal study was interpreted as showing extrinsic pressure on the posterior gastric wall consistent with a pseudocyst. After transfer from the medical to the surgical service a diagnostic peritoneal tap was performed. The ascitic fluid was clear and straw colored with an amylase of 343, lipase 14, albumin 2.4 gm%, and total protein 3.0 gm%. Acid-fast stain of the ascitic fluid was negative. On September 9, 1967, the patient underwent laparotomy. Massive ascites meas-

From the Department of Surgery, Veterans Administration Hospital, Bronx, N. Y., Albert Einstein College of Medicine, Bronx, N. Y., and the Mount Sinai School of Medicine, New York, N. Y.

uring 5500 cc's was encountered. A thick-walled pseudocyst was located directly posterior to the stomach; its estimated size was $6 \times 6 \times 4$ inches. Its contents were murky brown, but thin and watery in consistency. The peritoneum was extremely hyperemic. Before opening the cyst, a mixture of methylene blue and peroxide was injected into the cavity, but no dye was seen to escape. Hypaque® was then injected, and no communication was demonstrated, either to a major pancreatic duct or to the free peritoneal cavity. Following a biopsy of the cyst wall, negative for tumor, a posterior cystogastrostomy was performed. The liver, which was grossly normal, was then biopsied. The remainder of the abdominal exploration was negative, including the head of the pancreas, common bile duct, and gall bladder. The report of the liver biopsy was "focal fibrosis, mild." The postoperative course was uneventful with complete resolution of the ascites. When seen in the clinic three months following surgery, the patient had no complaints.

Discussion

A review of the literature (Table I) reveals certain features which should alert the clinician to the possibility that the ascites may be pancreatic in origin; namely, massive ascites in young alcoholics associated with marked

TABLE I

Case	Author	Treatment	Results
1	Schmidt & Whitehead	Posterior cystogastrostomy	Improved—Discharged 10th p.o. day
2	MacLaren et al	Pancreatico-gastrostomy	Discharged in 10 days
3	Wagner & Tolins	Pancreatico-gastrostomy	Improved
4	Cameron et al	Sphincterotomy, caudal pancreatectomy	Improved
5	Burrows & Poll	Combination of internal and external drainage	Improved 2 months
6	Smith	Marsupilization then reexploration	In 2½ years. Recurred—Improved
7	Barua et al	Laparotomy	Discharged 5 months—Improved
8	Barua et al	Peritoneoscopy and laparotomy	No follow-up
9	Barua et al	Peritoneoscopy	Died. Autopsy: Chemical peritonitis, relapsing pancreatitis, 2 pancreatic pseudocysts
10	Barua et al	Peritoneoscopy	Improved 3 months
11	Jensen & Babior	Observation only	Died of sepsis from lungs on 51st day chronic pseudocyst found at autopsy
12	Howard & Jordan	Necroscopy	Chronic pancreatitis with pseudocyst of pancreas which had perforated into the peritoneal cavity resulting in generalized peritonitis

weight loss and abdominal pain. Associated pleural effusions and a suggestive barium meal study further confirm the diagnosis. Proper examination of the ascitic fluid however, is the most accurate diagnostic method yet available and should be positive in every case.

Salient features of the twelve reported cases are of interest. Ages ranged from 25 to 52, with a mean of $34\frac{1}{2}$ years. Nine of the 12 patients were male. Alcoholic intake was heavy in 11 patients, unreported in the 12th. Weight loss was significant in 11 ranging from 20 to 65 pounds. Abdominal pain was noted in all patients. No specific characterization was apparent. Indirect x-ray signs were suggestive of pseudocyst in only 4 of 12 cases. Pleural effusions were present in 6 of 12. Ascitic fluid studies when performed suggested the diagnosis in every case. The most characteristic features included elevated albumin (exudate as opposed to a transudate), and elevations of the ascitic fluid amylase (previously reported) and lipase (not previously reported). In this case the ascitic fluid lipase was extremely elevated, whereas the amylase was only slightly elevated; a frequent phenomenon long known to occur in serum determinations during bouts of pancreatitis. The liver in each case reported was not sufficiently cirrhotic to account for the ascites.

Six of the 12 patients underwent some type of definitive surgery. All were immediately relieved of the ascites, though in the patient who underwent marsupilization (Case 6) the ascites recurred in $2\frac{1}{2}$ years. It should be noted that marsupilization is rarely performed for pancreatic pseudocyst today. Three of the six patients who did not undergo definitive surgery died. All deaths were directly related to the pseudocyst. One of the other untreated patients had no follow-up.

Summary

Ascites in an alcoholic is not always secondary to portal hypertension. A case of ascites secondary to a pancreatic pseudocyst is reported in which the diagnosis was aided by determination of the ascitic fluid lipase.

A clinical picture of a young alcoholic with massive ascites accompanied by abdominal pain, weight loss, and pleural effusion should suggest that the ascites may be pancreatic in origin. The diagnosis may be confirmed by studies of the ascitic fluid.

Surgical intervention is mandatory when the ascites is secondary to a pseudocyst.

The mechanism of the ascites associated with pancreatic disease has not as yet been elucidated; however, it is thought to represent an exudative response to leaking activated pancreatic enzymes.

References

1. Smith, E. B.: Hemorrhage Ascites and Hemothorax Associated with Benign Pancreatic Disease, *Arch Surg* 67:52, 1953.
2. Barua, R. L., Vella, F., and Steigman, F.: Massive Ascites due to Pancreatitis, *Am J Digest Dis* 7:900, 1962.

3. Burrows, L., and Poll, M. D.: Massive Ascites Secondary to Pancreatitis, *J Mt Sinai Hosp* 33:399, 1966.
4. Cameron, J. L., Anderson, R. P., and Ziudema, G. D.: Pancreatic Ascites, *Surg, Gynec & Obst* 125:328, 1967.
5. Howard, J. M., and Jordan, G. L.: *Surgical Diseases of the Pancreas*, Philadelphia: 1960 J. B. Lippincott, Co., Inc.
6. Jensen, M. M., and Babior, B. M.: Ascites due to Chronic Pancreatitis, *JAMA* 201:228, 1967.
7. McLaren, I. F., Howard, J. M., and Jordan, G. L.: Ascites Associated with a Pseudocyst of the Pancreas, *Arch Surg* 93:301, 1966.

Received for publication on December 3, 1968

Mesenteric Vascular Occlusion

RAGHAVENDRA VIJAYANAGAR, M.D., STEPHEN H. TOLINS, M.D. AND
PHILIP COOPER, M.D.

Although mesenteric vascular occlusion had been described as a clinical entity over a century ago by Tiedeman (1) in 1843, there has been little improvement in its high mortality rate (80-85%). It was not until Klass (2) in 1951 reported the first successful superior mesenteric artery embolectomy, that treatment other than wide resection of gangrenous bowel, with its attendant poor prognosis, was recognized as an approved therapeutic approach. Since then, a number of cases of successful superior mesenteric artery embolectomy have been reported (3-10). Case reports of emergency thromboendarterectomy and vascular reconstructive surgery of the superior mesenteric artery have recently appeared (11, 12). The purpose of this communication is to review the cases of mesenteric vascular occlusion treated at our institution, and to follow with a brief review of the literature. It is hoped that this retrospective analysis, added to others, will help to bring about needed improvement in the treatment of mesenteric vascular occlusion with its high mortality rate.

Material and Results

During a 14-year period from 1952 to 1966 there were 35 cases of mesenteric infarction treated at the Bronx Veterans Administration Hospital. The average age of the patients was 61 years, ranging from 38 to 80. All were male patients. Of the 35 cases, the diagnosis was confirmed by autopsy alone in 19; by operation alone in 8, and by both in 8 patients. Autopsy thus accounted for 77% of the diagnoses. Only 4 patients survived treatment and 31 were dead, a mortality of 88.5%. A correct preoperative diagnosis was made in 16 or 45.7% of the cases (Table I). Of the 16 cases, 6 patients were not operated upon because of severe cardiac failure, extreme shock or other diseases that made surgery appear unwise. One patient suffered a cardiac arrest in the operating room. Preoperative diagnoses other than mesenteric infarction, such as small bowel obstruction, perforated appendix, and pancreatitis, were made in 7 patients. Of the 23 patients with a preoperative diagnosis, 17 patients underwent exploratory examination. The details of the operative findings and the operation are listed in Table II. Three patients who underwent superior mesenteric artery embolectomy required bowel resection later because of inevitable gangrene, although effective circulation had apparently been established by this procedure. Anticoagulants were used in all three. One patient who underwent extensive bowel resection with the upper 30 cm of the jejunum anastomosed to the mid-transverse colon, had postoperative diarrhea and

From the Department of Surgery, Veterans Administration Hospital Bronx, New York, N. Y., Albert Einstein College of Medicine, Bronx, New York, N. Y., and the Mount Sinai School of Medicine, New York, N. Y.

TABLE I
Diagnosis Made in 23 of 35 Cases

Patient Category	No.	Per Cent
Correct preoperative diagnosis.....	16	45.7
Preoperative diagnosis other than mesenteric infarction.....	7	20.0
Diagnosis totally unsuspected.....	12	34.3
Diagnosed but not operated.....	6	17.1
Diagnosed and operated.....	17	48.6

difficulty in gaining weight. Although he was doing well, he died two months later of generalized embolization and cardiac failure.

A careful attempt was made to find the site of vascular occlusion from operative and autopsy records. Of the 35 cases, 25 or 71.4% had thrombosis or embolism of the superior mesenteric artery; 2 patients had in addition thrombotic occlusion of the inferior mesenteric artery; and 10 cases or 28.5% had thrombosis of the mesenteric veins. In the analysis of these cases we were interested in the approximate time relation between occlusion of the vascular system and gangrene of the bowel. The onset of vascular occlusion was taken as coincident with the appearance of abdominal pain and the end result of the occlusion calculated at the time of operation or death of the patient. In the latter cases, gangrene of the bowel was confirmed by autopsy (Table III). Of the 35 cases only one patient had been explored within 24 hours and in spite of superior mesenteric artery embolectomy, gangrene of the bowel developed. The remainder of the cases over 24 hours had gangrene of the bowel. Thus, the time relation from occlusion to gangrene of the bowel is critical.

An analysis of the symptomatology revealed that 91.4% of the patients suffered acute abdominal pain; 67.7% nausea and/or vomiting. Terminal shock and/or convulsions and coma were present in 67.7% of the cases (Table IV). Predisposing and/or associated diseases such as myocardial damage, arteriosclerotic heart disease, hypertension, auricular fibrillation and congestive heart failure were present in 25 or 71.4% of the cases (Table V). An interesting observation although limited in number of cases is the 25.7% incidence of venous thrombosis associated with carcinoma. The radical surgery and postoperative radiation may have been responsible for the sluggish circulation and thrombosis.

Discussion

Mesenteric vascular occlusion is a clinical disease consisting of any one of three different pathological entities; mesenteric arterial embolism, arterial thrombosis, or venous thrombosis. There is little difference in the clinical findings of these conditions (13, 14). Each presents as an acute abdominal catastrophe, with sudden severe upper or periumbilical pain in general associated with vomiting, diarrhea, distension and terminally, peripheral vascular

TABLE II
Operative Data in 17 Cases

No.	Findings	Operation	Result	Comments
1	Mesenteric infarction	Small bowel resection and anastomosis	Lived	
2	with segmental			
3	gangrene of small bowel			
4	Mesenteric infarction	Extensive small bowel resection	Died	Postoperative shock and death
5	with extensive gangrene of small bowel			
6				
7	Mesenteric infarction	Exploratory laparotomy and closure	Died	Resection of the involved bowel incompatible with life
8	with gangrene of entire small bowel up to mid-transverse colon			
9				
10	Embolism of the	Superior mesenteric artery embolectomy with revascularization of mesentery. Later bowel resection for inevitable gangrene	Died	One pt died of postoperative shock, and one pt did well but died 2 days later of cerebral embolization; 3rd pt died with congestive heart failure. Anticoagulants used in all 3
11	superior mesenteric			
12	artery			
13	Thrombosis of superior mesenteric artery. Thrombosis aorto-iliac area. Thrombosis of inferior mesenteric artery with gangrene of small bowel to mid-transverse colon	Aorto-iliac and inferior mesenteric artery thromboendarterectomy. Extensive bowel resection	Died	Postoperative shock and death. Autopsy showed gangrene of remaining colon
14	Missed diagnosis	Appendectomy and closure	Died	Autopsy showed thrombosis of superior mesenteric artery and gangrene of entire small bowel
15	Thrombosis of arteries to ileum with gangrene	Resection of entire ileum and jejunocolostomy	Died	Thrombosis resulted because of severe arteritis
16	Thrombosis of superior mesenteric artery	Resection of entire small bowel up to mid-transverse colon and anastomosis of upper $\frac{1}{3}$ th of jejunum to transverse colon	1 Died	One death was due to shock. The 2nd pt lived for more than 2 mos and died later of generalized embolization
17	with gangrene of small bowel and colon to mid-transverse		1 Lived	

TABLE III
Analysis of Time Relation and Findings

Duration	No.	Findings
Within 24 hours	1	Exploratory laparotomy revealed dusky bowel. Superior mesenteric artery embolectomy was without effect and a bowel resection was done
24-48 hours	17	2 Pts had ? gangrene of bowel and superior mesenteric artery embolectomy was not helpful and a bowel resection was done. Remainder of cases had gangrene of bowel
48-72 hours	12	All had gangrene of bowel
Unknown	5	Gangrene of bowel
Total	35	

TABLE IV
Symptomatology

Symptoms	No. Cases	Per Cent
Abdominal pain.....	32	91.4
Nausea and/or vomiting.....	23	67.7
Constipation.....	9	25.7
Diarrhea.....	7	31.4
Bloody stools.....	4	11.3
Terminal shock and/or convulsions and coma.....	23	67.7

TABLE V
Predisposing and/or Associated Diseases

Type	No. Cases	Per Cent
Myocardial damage, A.S.H.D., hypertension, auricular fibrillation and congestive heart failure.....	25	71.4
Generalized arteriosclerosis, including C.V.A., and P.V.D.....	11	31.0
Carcinoma.....	9	25.7
None.....	2	

collapse. Embolic occlusion is usually associated with auricular fibrillation or post-myocardial infarction mural thrombi. Patients with superior mesenteric artery thrombosis usually have had the symptom complex of "abdominal angina" for weeks or months prior to complete occlusion (11, 12, 14-16). Venous thrombosis may be primary, or secondary. In the latter case, blood dyscrasias or conditions of the lower abdomen are the principle causes (13). Occlusion of the peripheral mesenteric vessels may be due to multiple small emboli, arteritis, or arterial spasm secondary to central or peripheral vascular collapse (14, 17). By far the most common is the occlusion of the superior mesenteric artery and the most rare is the occlusion of the inferior mesenteric

artery (18, 19). Thrombosis of the superior mesenteric vein comprises 15–25% of all mesenteric vascular occlusion (13). The anatomical disposition of the superior mesenteric artery predisposes to the lodging of an embolus. It is roughly one centimeter at its origin and gradually reduces to 0.8 cm in diameter at its termination and makes an angle of 30° at its origin from the abdominal aorta (4).

The early diagnosis of this condition is essential for successful treatment. Sudden, severe, upper or midabdominal pain associated with nausea and vomiting, passage of bloody stools in a patient who has auricular fibrillation, should make one suspect embolic occlusion of the superior mesenteric artery. A previous history of "abdominal angina" and symptoms associated with generalized arteriosclerosis should give a clue to the diagnosis of superior mesenteric artery thrombosis (11, 20). The disparity between the severity of symptoms and the minimal physical signs should be kept in mind. Abdominal distention, severe tenderness, and muscle guarding are late signs of the disease. Marked leukocytosis with a shift to the left is a constant finding. The degree of leukocytosis depends upon the ischemia and inflammatory reaction of the bowel. Abdominal paracentesis usually reveals a serosanguinous fluid. Diagnosis obtaining different radioactive curves from the abdominal wall following the intravenous injection of I^{131} -labelled human serum albumin awaits a clinical trial (21). An electrocardiogram is essential to understand the status of the heart. Roentgenologic examination is important although of little significance in the initial stages. There is diminution in the amount of gas in the intestines caused by severe spasm of the bowel. Later in the disease process x-ray study shows a picture of adynamic ileus as gas dilates small and large bowel up to the splenic flexure, and there is no obstruction to a barium enema (22, 23). A barium swallow may show stasis of barium in the small bowel, edema of the bowel wall with ulceration of the mucosa. In selected cases aortography may be of value.

The treatment is rapid fluid and electrolyte replacement and exploratory laparotomy. Superior mesenteric artery embolectomy, thromboendarterectomy, reimplantation of the superior mesenteric artery into the abdominal aorta, aortomesenteric by-pass graft distal to the obstruction, resection of the involved bowel and end-to-end anastomosis are the surgical procedures available (2, 5–8, 10–12, 19). The result of superior mesenteric artery embolectomy or thromboendarterectomy depends upon the time interval between occlusion and operative intervention. The patency of celiac and inferior mesenteric arteries and their anastomosis are a major factor (12, 24). Reiner (24) has demonstrated by injection studies of the mesenteric arterial circulation that there is abundant arterial anastomosis and the intestinal infarction is not necessarily due to cessation of blood flow but rather to its critical reduction. It is the amount of hemorrhage, stasis of blood in the intramural vessels, bacterial infection, and absorption of endotoxin which make peripheral vascular collapse more evident than the intestinal infarct (25, 26). The more time elapsed before revascularizing the mesenteric circulation, the more diffi-

cult is the postoperative management. The amount of hemorrhage, bacterial infection, absorption of endotoxin and hyperpotassemia after revascularization of the mesenteric circulation are dependent upon the amount of damage to the bowel wall (25-28). Extensive resection of the bowel in the late cases of mesenteric vascular occlusion has been followed by very high operative mortality and an almost hopeless prognosis. Even in many cases of successful superior mesenteric artery embolectomy there is a problem of malabsorption syndrome in the later period (7, 8). The best results are obtained by immediate exploratory laparotomy, reestablishment of mesenteric circulation if possible, resection of the nonviable bowel and a very careful postoperative management utilizing blood transfusions, antibiotics, maintenance of electrolyte balance and anti-coagulants as indicated.

Summary

The occurrence of mesenteric infarction at the Bronx Veterans Administration Hospital during a 14-year period was analyzed. There were 35 cases during this period and autopsy accounted for 27. Only four patients survived treatment. The approximate time relation between vascular occlusion and gangrene of the bowel was estimated and found to be critical. Twenty-five patients had associated arteriosclerotic heart disease or hypertension. A brief review of the subject is given.

References

1. Cited by Orr, T. G. et al: Mesenteric Vascular Occlusion, *JAMA* 155:648, 1954.
2. Klass, A. A.: Embolectomy in Acute Mesenteric Occlusion, *Ann Surg* 134:913, 1951.
3. Atwell, R. G.: Superior Mesenteric Artery Embolectomy, *Surg Gyn Obst* 112:257, 1961.
4. Miller, H. L., et al: Mesenteric Infarction, *N Eng J Med* 259:572, 1958.
5. Rutledge, H. R.: Superior Mesenteric Artery Embolectomy, *Ann Surg* 154:529, 1964.
6. Saris, S. D., et al: Superior Mesenteric Artery Embolectomy, *Arch Surg* 81:108, 1960.
7. Stewart, G., et al: Superior Mesenteric Artery Embolectomy, *Ann Surg* 154:274, 1960.
8. Shaw, R. S.: Superior Mesenteric Artery Embolectomy in the Treatments of Massive Mesenteric Infarction, *N Eng J Med* 257:595, 1957.
9. Weaver, J. P. A., et al: Recovery of Intestinal Function after Successful Superior Mesenteric Artery Embolectomy, *Brit J Surg* 52:44, 1965.
10. Znidema, G. D.: Surgical Management of Superior Mesenteric Artery Emboli, *Arch Surg* 82:113, 1961.
11. Brittain, S. R.: Emergency Thromboendarterectomy of the Superior Mesenteric Artery, *Ann Surg* 158:138, 1963.
12. Mikkelsen, W. P.: Intestinal Angina: Its Surgical Significance, *Am J Surg* 94:262, 1957.
13. Manson, E. M.: Vascular Lesions Producing the Acute Abdomen, *Surg Clin N Am* 40:1241, 1960.
14. Shaw, R. S.: Vascular Lesions of the G.I. Tract, *Surg Clin N Am* 39:1253, 1959.
15. Meier, A. L.: Mesenteric Artery Occlusion with Intestinal Gangrene, *Arch Surg* 88:181, 1964.
16. Mandell, H. N.: Abdominal Angina, *New Eng J Med* 257:1035, 1957.
17. Herr, W.: Intestinal Gangrene without Apparent Vascular Occlusion, *Am J Surg* 110:231, 1965.
18. Carter, R.: Inferior Mesenteric Vascular Occlusion, A Sigmoidoscopic Diagnosis, *Surgery* 46:845, 1959.

19. Carter, R.: Acute Inferior Mesenteric Vascular Occlusion, A Surgical Syndrome, *Am J Surg* 98:271, 1959.
20. Keely, K. F.: Abdominal Angina Syndrome, *Gastroenterology* 37:480, 1959.
21. Absolon, B.: An Experimental Study of the Diagnosis of Mesenteric Infarction, *Surg Gyn Obst* 110:617, 1960.
22. Nelson, S. W.: Findings on Plain Roentgenogram of the Abdomen Associated with Mesenteric Vascular Occlusion, *Am J Roent* 83:886, 1960.
23. Wang, C. C., et al: Mesenteric Vascular Disease, *Am J Roent* 83:895, 1960.
24. Reiner, L., et al: Injection Studies on the Mesenteric Arterial Circulation, *Gastroenterology* 39:747, 1960.
25. Marston, A.: Causes of Death in Mesenteric Arterial Occlusion, *Ann Surg* 158:952, 1963.
26. Milliken, J.: A Study of the Factors Involved in the Development of Peripheral Vascular Collapse following Disease of Occluded Superior Mesenteric Artery, *Brit J Surg* 52:699, 1965.
27. Laufman, H.: Mesenteric Blood Vessels, *Advances in Surgery and Physiology*, *Arch Surg* 88:1021, 1964.
28. Liuhm, R. E.: Physiological Approach to Successful Treatment of Endotoxin Shock in the Experimental Animal, *Arch Surg* 78:116, 1959.

Received for publication November 21, 1968

Unusual Problems in Surgery

A. ROBERT BECK, M.D., AND JULIUS J. LEICHTLING, M.D., Co-Editors

CASE NO. 16

Recurrent Sacrococcygeal Teratoma with Rectal Fistula

Sacrococcygeal teratomas are tumors of more than one germ layer which occur in the region of the coccyx. The following case illustrates the consequences of inadequate initial treatment of this tumor and the subsequent successful management of the complications which developed.

An 11-year-old Santo Dominican girl was admitted to Elmhurst Hospital because of two draining sinuses in the sacral region. According to the parents, the patient had a "tumor" of the lower back removed during the newborn period. At one year of age a second operation was necessary because of an infection in the sacral area. A third operation was performed in Santo Domingo when she was 8 years of age for the same condition. Since that time the patient had had intermittent drainage of foul-smelling material from the sacral region. We were unable to obtain further information from the hospitals in which the previous operations were performed.

The child was a thin, well-developed, healthy young girl. The pertinent physical findings were limited to the sacral area. There was a well-healed vertical midline scar which extended from the coccyx to the anus. Purulent material could be expressed from two 3 mm openings in a second, transverse scar (Fig. 1). On rectal examination, a firm mass was felt displacing the rectum anteriorly. The mass lay behind the rectum and extended along the right posterior lateral pelvic wall. X-rays of the pelvis revealed a soft tissue retrorectal mass containing several calcifications (Fig. 2). Hypaque was injected into one of the draining sinuses and the subsequent roentgenograms demon-

strated extensive ramifications throughout the mass and communication with the rectosigmoid (Figs. 3, 4). Sigmoidoscopy was performed and a 0.5 cm area of induration and inflammation was seen at about 10 cm from the anus on the posterior rectal wall. Methylene blue was injected into one of the external sinuses and was seen to enter the rectum at this point. The rectal mucosa was otherwise normal. Barium enema, gastrointestinal, and small bowel contrast studies and an intravenous pyelogram were normal.

The patient was thought to have a recurrent, infected sacrococcygeal teratoma, with communication into the rectum. The tumor had probably been incompletely excised and the rectum entered at the first operation. This had established a continuing source of contamination of the operative area and thus the recurrent infections. The presence of a malignancy could not be excluded.

Excision of the mass and closure of the fistula into the rectum were to be performed during the same procedure. In order to divert the fecal stream from the proposed operative site, a preliminary transverse colostomy was performed. The tumor was removed one month later using a sacral approach. A transverse incision was employed and an ellipse of skin containing the two fistulae was removed. The tumor, which measured 6 x 8 x 5 cm was removed and the coccyx excised. The levators were identified by use of a nerve stimulator. A 0.5 cm opening into the rectum was identified, its margins excised and the defect closed with two layers of catgut. The wound was then closed in layers and drained. The tumor proved to be a benign (recurrent) teratoma containing solid and cystic areas (Fig. 5). Tissues of neural, lymphoid, respiratory, intestinal, and bony origin were present within the mass. (Fig. 6)

Four months later a barium enema and sigmoidoscopy were normal and the colostomy was closed. The sacral incision was well healed (Fig. 7).



Fig. 1. Sacral area at the time of admission. Note well-healed scars from previous surgery and areas of purulent drainage.

One year after excision of the tumor the patient was well and had no evidence of recurrence of the tumor or rectal fistula either by clinical or barium enema examination.

Sacrococeygeal teratoma is a rare tumor which occurs in approximately one in 40,000 live births and is found predominantly in females (80-90%) (1). Although primarily a tumor of infancy, cases have been reported in the fifth decade of life (2).

The pathogenesis remains obscure but most authors believe that the tumor arises from a nidus of multipotential cells, the primitive knot, at the

tip of the involuting tail. Such a theory best fits the clinical observations and is embryologically acceptable since a tail is transiently present in the human embryo during the sixth week of development. During subsequent growth and differentiation, resorption of the tail takes place and the coccyx is formed. The middle sacral artery and vein persist as the blood supply to this rudimentary tail (3). As one would therefore expect, the principal blood supply to a teratoma arising in the sacrococeygeal area is derived from these vessels.



Fig. 2. X-ray of the pelvis showing a soft tissue density which contains calcifications (arrows).

Although the tumor usually presents as a globular mass in the sacral area and is obvious at birth, several variations do occur. A small number of tumors have a long fibrous pedicle attached to the coccyx. Surgery consists simply of division of the pedicle since it contains no tumor tissue. The usual sacrococcygeal teratoma lies mainly externally and may be large enough to displace the anal opening. Various degrees of intrapelvic extension are found; some tumors lie almost entirely within the pelvis and present very little external evidence of their presence.

The tumor may be cystic or solid and may contain glial tissue, choroid plexus and peripheral nerve; cardiac,

smooth and skeletal muscle; embryonal and adult fat; mucous, sweat and sebaceous glands; stratified squamous, columnar and respiratory epithelium; fibrous and connective tissue; hair follicles; pancreatic tissue; cartilage, and bone. Occasionally well-formed organs are found. Most authors agree that about one-third of sacrococcygeal teratomas are malignant. Although any element of the tumor may become malignant, the most frequently found malignancy is adenocarcinoma. Most malignant tumors are intimately attached to the coccyx and have a dumb-bell portion extending a variable distance into the pelvis, or are primarily intrapelvic with a minimal of external



Fig. 3. Sinogram. Hypaque was injected into a draining sinus in the sacral area. Extensive ramifications are noted within the mass.

growth (1). The clinical features which differentiate malignant from benign teratomas have been found to relate closely to the age of the patient at the time of discovery of the tumor and to the presence or absence of symptoms of bowel or bladder obstruction (4). The majority of benign sacrococ-

cygeal teratomas produced no functional difficulties even when there is considerable intrapelvic extension. Progressive growth, filling the whole pelvis may cause mild obstructive symptoms. When the obstruction is severe, the tumor is usually malignant and involves the presacral nerve plexus



Fig. 4. Lateral view of simultaneous sinogram and barium enema. Note anterior displacement of the rectum. The hypaque injected into the sinus enters the rectum posteriorly.

and the visceral walls. Bowel or bladder dysfunction, pain on defecation, discomfort during standing and particularly the presence of vascular or lymphatic obstruction all suggest the diagnosis of malignancy. In one series of 79 teratomas presenting as a mass at birth, 8 were malignant or later became malignant (an incidence of

10%). In contrast, 22 out of 24 tumors discovered after the age of 2 months were malignant (4).

In another series, only 7% of 56 teratomas removed from patients less than 4 months of age showed malignant changes. In contrast, 42% of 31 teratomas which were removed from children between 4 months and 15

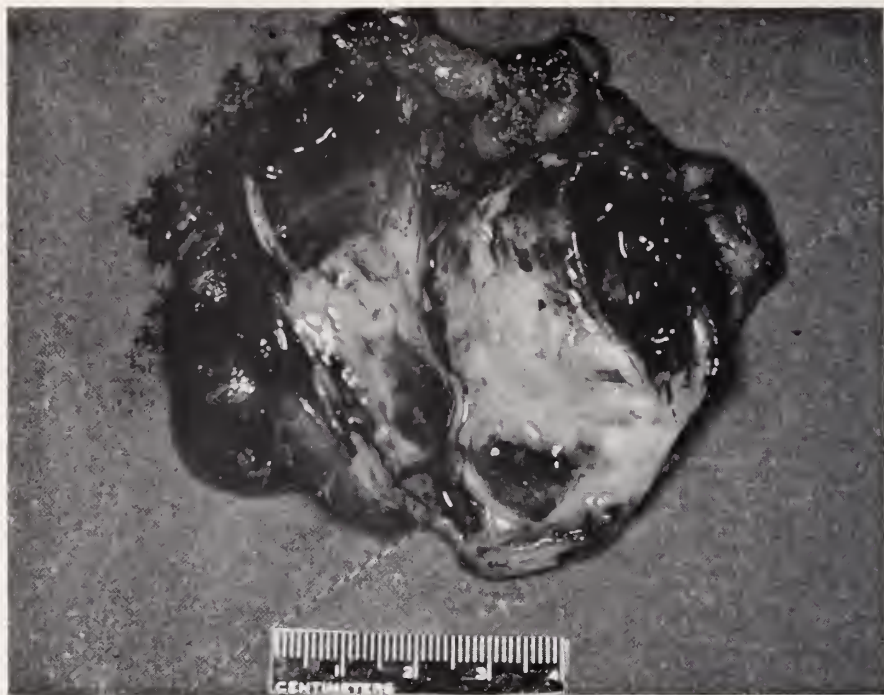


Fig. 5. Cut surface of resected tumor showing solid and cystic areas.

years of age had malignant changes (2). It is of interest that in a combined group of 27 teratomas which were discovered at birth but were not operated on until the age of 4 months, 18 (67%) remained benign and only nine (33%) were malignant (4). This leads one to believe that the high incidence of malignancy in infants operated upon after one month of age is not entirely due to malignant change which takes place in a benign tumor. The malignant tumors are largely intrapelvic and may not be discovered until they cause symptoms some time after birth. The prognosis of malignant teratoma is extremely poor.

In children, sacrococcygeal teratoma must be differentiated from dermoid cyst, anterior myelomeningocele, lipoma, perirectal abscess, cystic hy-

groma, sarcoma, and angioma. Meningoceles are always cystic. Neurological defects as well as bone deformities are commonly found. Rarely does the sacrococcygeal teratoma extend into the spinal canal and cause neurological symptoms. A pilonidal cyst or sinus is frequently mistaken for a sacrococcygeal teratoma. However, pilonidal cysts are much more common in the adult male than in the female infant or child and presacral extension does not occur. Barium enema and intravenous pyelography should always be done. X-ray examination of the tumor demonstrates calcification in 35% of cases.

Surgery consists of early and complete excision of the tumor and the coccyx. A chevron incision affords better exposure than a vertical incision.

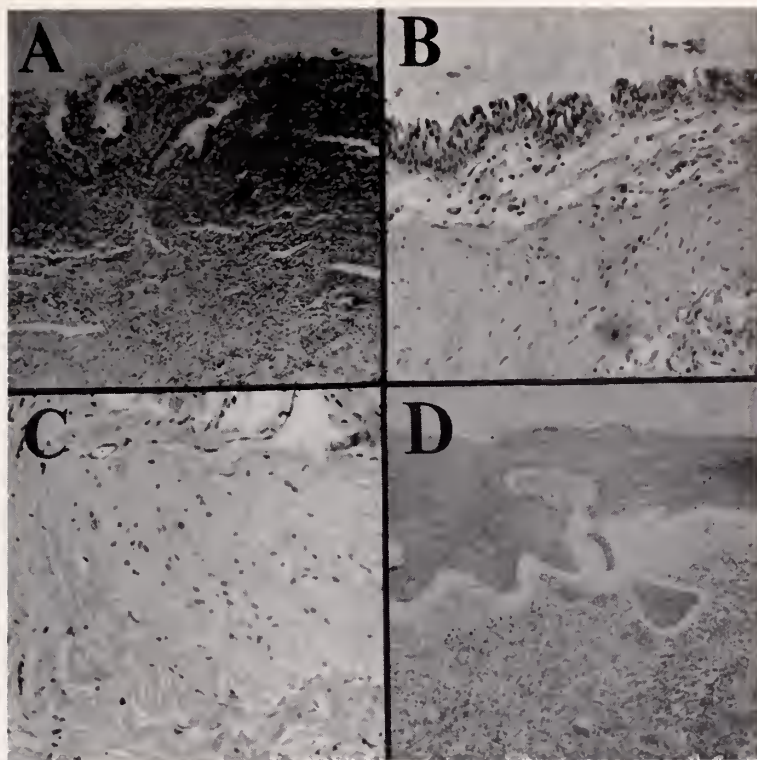


Fig. 6. Microscopic examination of the tumor showed intestinal mucosa (A), respiratory epithelium (B), neural tissue (C), bone (D), and lymphoid tissue.

Wound infections occur more frequently in those patients with a vertical incision because the lower pole of the incision is very close to the anus (1). If the tumor is an external one with little or no pelvic extension, the patient is placed in the prone position and an inverted V incision is made. The sacrum can then be divided at the 4th or 5th sacral segment. The middle sacral artery and vein are located immediately ventral to it and can be ligated and divided. Skin flaps are then developed around the tumor and the mass removed en bloc with the coccyx. A single two-stage operation is recommended for tumors with large retrorectal extension into the pelvis and

abdomen (3). The first stage is completed through a midtransverse suprapubic incision. An extraperitoneal dissection can be carried down to the origin of the middle sacral artery and vein, which are ligated and divided. The intraperitoneal extension of the tumor can then be dissected free without excessive blood loss. The abdomen is closed, the patient is placed in the prone position and the usual inverted V shaped incision is made in the sacral area.

Two occurrences are to be feared: inadequate blood replacement during the operation and incomplete removal of the tumor. In the most recently reported series 9 operative deaths oc-



Fig. 7. One year after resection of the tumor, there was no recurrence of the tumor or fistula.

curred in 73 operations for benign teratomas; 6 of these were caused by overwhelming blood loss (4). The total operative mortality was 12%. Removal of the coccyx is essential since in nearly every case teratoma is intimately associated with its anterior surface. Incomplete removal of the coccyx results in a recurrence rate of 30% (4). The importance of prompt diagnosis and treatment cannot be overemphasized. If surgery is performed when the child is older than one month of age the surgical mortality is more than doubled, the mortality from benign recurrence is doubled and the mortality due to malignant recurrence is increased fivefold (1).

Benign recurrence of a sacrococcygeal teratoma is common. The usual cause of recurrence is incomplete removal of the tumor, particularly fail-

ure to remove the coccyx. Successful outcomes have resulted after two or three excisions. However, there are several cases on record where a benign tumor became malignant after the second or third recurrence and eventually caused the death of the patient (2).

Our case illustrates several important points. Careful and complete excision of the tumor performed at the first operation will help to eliminate subsequent complications. We assume that an undetected injury to the posterior rectal wall had occurred. Surgery confirmed that the coccyx had not been removed. These factors accounted for the tumor recurrence and infection. The two subsequent operations failed because they apparently consisted of incision and drainage of the infected area and did not deal with

the underlying cause. We felt that a diverting colostomy was an essential preliminary in the treatment of the chronic rectal fistula because it would keep the operative area free of stool, allow the fistula to heal undisturbed, and also decrease the chance of a wound infection. Avoidance of damage to the levators during removal of the tumor was aided by the use of a nerve stimulator.

Summary

1. A case of recurrent benign sacrococcygeal teratoma complicated by a rectal fistula is presented and its management discussed.

2. The entity of sacrococcygeal teratoma is reviewed.

A. Robert Beck

References

1. Benson, C. D., et al, ed: *Pediatric Surgery*, Chicago: Year Book Medical Publishers, 1962, pp. 849-854.
2. Waldhausen, J. A., Kilman, J. W., Vellios, F. and Battersby, J. S.: Sacrococcygeal Teratoma, *Surgery* 54(6): 933, 1963.
3. Smith, B., Passaro, E., and Clatworthy, H. W., Jr.: The Vascular Anatomy of Sacrococcygeal Teratomas: Its Significance in Surgical Management, *Surgery* 49(4): 534, 1961.
4. Donnellan, W. A., and Swenson, O.: Benign and Malignant Sacrococcygeal Teratomas, *Surgery* 64(4): 834, 1968.

Received for publication November 28, 1968

CLINICO-PATHOLOGICAL CONFERENCE

Gastrointestinal Bleeding

Edited by

FRANKLIN M. KLION, M.D.

A 66-year-old white man was admitted to The Mount Sinai Hospital for the 16th time because of increasing edema and shortness of breath.

Twenty-three years before, a thoracolumbar sympathectomy had been performed for hypertension. Following the operation his blood pressure returned to normotensive levels. Chronic atrial fibrillation was controlled with digitalis. He was hospitalized twice for bronchopneumonia which responded to penicillin, and on two other occasions for syncopal episodes believed to be due to a "sensitive carotid sinus." Six years prior to admission he experienced shortness of breath and dyspnea on exertion, which improved on a rigid low salt diet and diuretic therapy. Several uric acid calculi were removed from his bladder and a suprapubic prostatectomy was performed for benign prostatic hypertrophy. The hemoglobin on admission was 9.6 gm%, blood urea nitrogen 36 mg%, fasting blood sugar 102 mg%, creatinine 2.1 mg%, and uric acid 6.3 mg%. Seven months later he again noted hematuria. Cystoscopy and a left retrograde pyelogram were normal. The following year he was readmitted for progressive shortness of breath and tarry stools. The blood pressure was 130/70, pulse 70 min and irregular. The ocular fundi were normal. The neck veins were distended and crepitant rales were heard in both lung bases. A high pitched Grade 3 systolic murmur was audible at the apex and aortic area, which radiated to the neck and left axilla. The liver was palpated five finger-breadths below the right costal margin, and there was marked pitting edema of the lower extremities. The hemoglobin was 6.4 gm%, the white blood count 7,700/mm³ with a normal differential count. The blood urea nitrogen was 60 mg% and the serum creatinine 3.1 mg%. The serum bilirubin, electrolytes, transaminase, alkaline phosphatase activity and prothrombin time were normal. The serum albumin was 3.6 gm% and globulin 2.5 gm%. Paper electrophoresis of the serum showed a decreased albumin and gamma globulin. The urine contained a trace of protein and the sediment showed 1-3 red blood cells per high power field. An electrocardiogram showed a left bundle branch block pattern, and frequent ventricular premature contractions. An x-ray examination of the upper gastrointestinal tract was normal. He improved with multiple blood transfusions and iron therapy.

He was readmitted several weeks later for additional transfusions of blood following the passage of mahogany-colored stools. The physical examination was unchanged except for minimal ascites, and bilateral coarse rhonchi and wheezes. The vital capacity was 49% of normal. Following a fourth episode of gastrointestinal bleeding, he underwent an exploratory laparotomy. Two small ulcerations in the jejunum were suture ligated, and a pyloroplasty was

performed. A jejunal biopsy specimen was normal. Postoperatively, he continued to have rectal bleeding and was admitted on several occasions for blood transfusions. The hemoglobin ranged between 7-9 gm%. The blood urea nitrogen was 95 mg%. X-ray examinations of the upper and lower gastrointestinal tract were normal.

Two months prior to his final admission, chest pain and increasing dyspnea developed. He appeared acutely and chronically ill. The neck veins were distended at 45 degrees and hepatojugular reflux was elicited. The blood pressure was 98/66, the pulse varied between 40-52 per minute and was irregular. The respirations were 20 per minute. The lungs were clear and the cardiac murmur was unchanged. There was shifting dullness on percussion of the abdomen and a fluid wave was elicited. The liver edge was palpated five fingerbreadths below the right costal margin. There was marked edema of the lower extremities. The hemoglobin was 7.8 gm%, the white blood count 6,000 mm³ with 74% neutrophils, 15% band forms, 6% lymphocytes, and 5% monocytes. The platelet count was 69,000/mm³. The blood urea nitrogen was 112 mg% and creatinine 2.8 mg%. The serum electrolytes were normal. A stool examination was guaiac positive. An electrocardiogram showed atrial fibrillation with an advanced A-V block.

He received blood, digitalis, and diuretic therapy, and following implantation of a cardiac pacemaker, he was discharged. Despite therapy he continued to gain weight and he was readmitted one month later. The hemoglobin was 7.5 gm%, blood urea nitrogen 101 mg%, creatinine 2.6 mg%, serum albumin 1.7 gm%, and globulin 4.6 gm%. The sodium was 133 mEq/L, potassium 4.0 mEq/L, chlorides 102 mEq/L, and carbon dioxide 21 mEq/L. The serum bilirubin, scot, prothrombin time and calcium were normal. He failed to improve with additional blood replacement, digoxin or diuretic therapy, and expired on the tenth hospital day following a massive gastrointestinal hemorrhage.

*Dr. Jerome Wayne**: This 66-year-old man had hypertension, nephrolithiasis, renal insufficiency, heart disease, ascites, and gastrointestinal bleeding. Can one disease explain all or most of the clinical picture, or did he have several unrelated diseases? There are two diseases which account for the entire clinical picture. Gastrointestinal bleeding is frequent in the Grönblad-Standberg syndrome or pseudoxanthoma elasticum. Most of the symptoms are a result of widespread degeneration of elastic fibers. In addition to gastrointestinal bleeding, other vascular manifestations include hypertension, arterial calcification, coronary insufficiency, and changes in the peripheral pulses. Arteritis with involvement of the kidneys also is occasionally seen. The diagnosis, however, is difficult if not impossible to establish without two of the cardinal manifestations of the disease. One of the so-called angioid streaks of the optic fundi are actually cracks in Bruch's elastic membrane of the choroid, and have a distribution similar to the vascular pattern.

*Senior Clinical Physician, The Mount Sinai Hospital; Associate in Medicine, Mount Sinai School of Medicine of The City University of New York, New York.

The second is a loss of elasticity of the skin. When the skin is pinched the cutaneous fold produced is sustained for a considerable period of time. Eventually the skin assumes a "plucked chicken" appearance with multiple small, yellowish papules due to degeneration of the elastic fibers. It is from these papules that the syndrome was named "pseudoxanthoma." These two lesions occur together in about 60 percent of the patients. I do not think this disease process was present because of the long hiatus between his hypertension and other symptoms, the absence of angioid streaks or cutaneous manifestations, and the severity of his heart disease.

The second disease which might explain all or most of the picture is amyloidosis. Arterial hypertension may occur in amyloidosis although it is uncommon. The heart is also affected in amyloidosis and may be an obscure cause of refractory congestive heart failure. Can the renal involvement be explained by amyloidosis? Renal amyloidosis is more common in the secondary form of the disease, that is, secondary to some other illness. Primary amyloidosis of the kidneys has a more fulminant course. Could renal stones or obstructive uropathy explain the progressive azotemia? The retrograde pyelogram excluded bilateral obstructive uropathy. An attempt was made to visualize only one side because of the complications of bilateral ureteral catheterization. Since one functioning kidney is sufficient to prevent azotemia, the patient must have had diffuse renal disease. Nephrosclerosis resulting from prolonged hypertension is a possibility, and the history of hypertension preceding proteinuria certainly favors this diagnosis.

The combination of hepatomegaly and ascites suggests cirrhosis, carcinomatosis, congestive heart failure or hepatic venous occlusion. There was no evidence that he had a Chiari syndrome or cirrhosis. More important than the tests of liver function was the fact that he sustained multiple episodes of gastrointestinal bleeding without hepatic encephalopathy. Patients with primary carcinoma or metastatic carcinoma of the liver rarely live for six years after symptoms develop. I suspect, therefore, the hepatomegaly and ascites was due to congestive heart failure. However, hepatomegaly is also frequently seen in amyloidosis, and tests of liver function are usually preserved since the amyloid is deposited between the liver cells and sinusoids within the space of Disse. Hepatic dysfunction results when liver cells are compressed, and there is interference with blood-liver exchange. Portal hypertension has been reported in amyloidosis, but is rare, and all of the patients bled from esophageal varices. In one series of 103 patients with amyloid, ten had ascites. Although many features of the man's illness support amyloidosis, the uric acid stones, jejunal ulcerations, and thrombocytopenia remain unexplained, although the uric acid may have been caused by diuretic therapy. Diminished renal clearance causes decreased uric acid excretion, and a propensity to form stones.

The small bowel ulcerations may have been due to potassium supplementation. Ulcerations of the mucosa are believed to result from high local concentrations of potassium that occur when the tablets disintegrate on the mucosa.

Congested mucosa such as occurs in congestive heart failure is especially susceptible to the damaging effects of high potassium concentrations. These erosions heal by stenosis, and usually do not bleed. In any case I do not think he bled from these lesions. However, a clinically accurate method for establishing the exact site of gastrointestinal bleedings has not been found.

Whether melena occurs following gastrointestinal bleeding depends to some extent on transit time. In 1943, Schiff gave 100 to 200 ml of blood by nasogastric tube and produced tarry stools. One liter of blood produced a bloody stool if a bowel movement occurred within four hours. When the transit time was 20 hours, the stool was tarry. Hillsman instilled 200 cc of blood via a Miller-Abbott tube at various levels of the intestinal tract, and found melena could be produced by instillation of blood at all levels proximal to the ascending colon. Luke, a British surgeon, introduced various quantities of blood into the cecum at appendectomy, and found that melena occurred from the cecal area if the first movement occurred after 72 hours. When stools occurred less than 24 hours after the instillation of the blood, they were red. Therefore, melena can occur from cecal bleeding if the transit time is very slow; since blood is a stimulant of peristaltic activity, melena rarely results from bleeding from cecal lesions.

A nasogastric tube should be passed in all patients with gastrointestinal or rectal bleeding, to examine the contents of the stomach. Other useful methods to document the source of gastrointestinal bleeding include x-ray examination of the upper gastrointestinal tract and endoscopy. However, because of the difficulty in ascertaining the site of bleeding, more elaborate methods have been devised. Some clinicians pass a Miller-Abbott tube and hand-aspirate every 15 or 30 minutes. Unfortunately, blood in the gastrointestinal tract is not stagnant, so that aspirated blood may have originated several feet from the location of the tip of the tube. It will, however, differentiate bleeding to the upper or lower small bowel or large intestine.

Another method we have been using involves a string which has multiple radiopaque sutures. The string is swallowed by the patient and is left in place for about 4 to 12 hours. A flat film of the abdomen is taken to localize the string, and 20 cc of fluorescein is injected intravenously. If the patient is bleeding, the fluorescein will mix with the blood and stain the string. Four minutes later the string is removed and examined by ultraviolet light. Since the string will be marked by blood lost in the preceding four minutes the exact site of bleeding can be localized anatomically. Although the string test is not always successful, it has been helpful. I would place the site of bleeding in this patient somewhere proximal to the cecum and distal to the ligament of Treitz, since he did not have hematemesis.

He had a small bowel lesion associated with uric acid stones, ulcerations, gastrointestinal bleeding, low blood platelets, and perhaps amyloidosis. One can exclude most of the common small bowel tumors, of which leiomyoma is the most common, but also include lipomas, adenomatous polyps and hemangiomas. Excluding adenocarcinoma, lymphomas are the most common

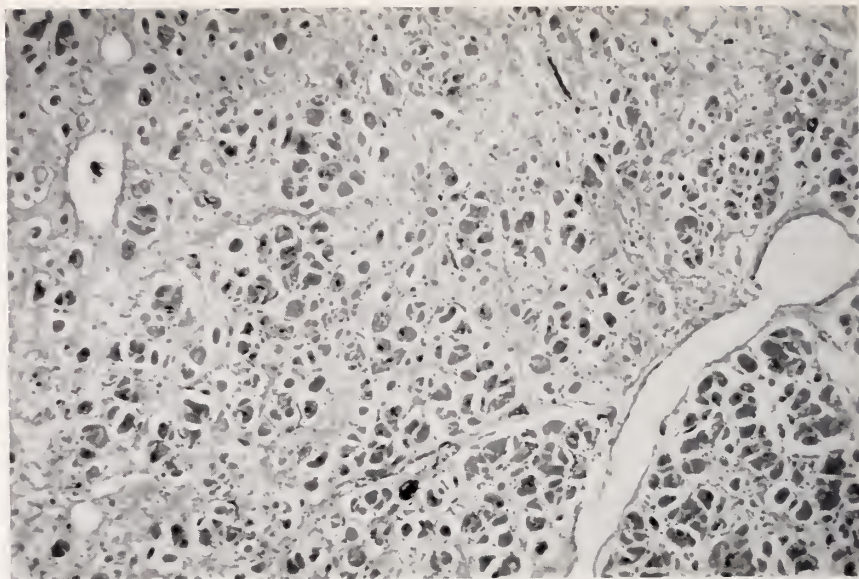


FIG. 1. Photomicrograph of heart showing diffuse atrophy of the myocardial fibers and interstitial fibrosis (H & E $\times 100$).

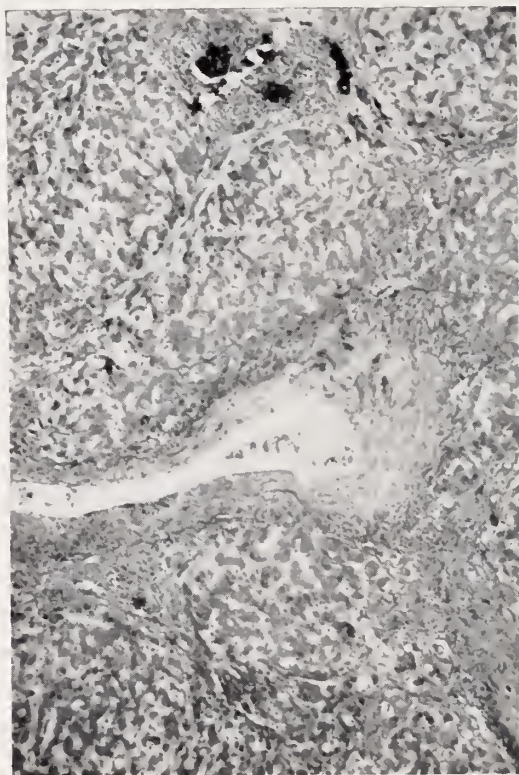


FIG. 2. Marked thickening of hepatic vein branches and early septa formation (Masson Trichrome $\times 40$).



FIG. 3. Multiple nodules of varying size within the small intestine. One shows a deep ulceration.

malignant small bowel tumors, and are associated with ulcerations and bleeding. In patients with isolated lymphomas, lymphosarcoma and reticulum cell sarcoma are the most frequent type. Hodgkin's disease rarely involves the small bowel. Renal calculi occur in about two percent of patients with lymphomas, which is only slightly greater than for the general population. However, the incidence of calculi is four percent in patients with lymphosarcoma with involvement of the bone marrow.

Finally, three percent of patients with generalized Hodgkin's disease have secondary amyloidosis. The duration of the disease usually ranges from 3 to 19 years prior to the development of amyloidosis. Many manifestations of this man's illness may be explained by amyloidosis secondary to lymphosarcoma involving the gastrointestinal tract and bone marrow.

Question: Do you think that the murmur heard in the neck and aortic area was representative of aortic stenosis associated with gastrointestinal bleeding?

Dr. Wayne: Aortic stenosis would not explain the constellation of signs and symptoms.

Dr. Kalmen Feinberg:* This patient had several diseases. Gross examination of the heart revealed a fibrinous pericarditis. The heart was almost twice the normal weight, and the left and right ventricles were dilated. The aortic valve was slightly stenotic and there were calcifications at the base of the semilunar valve. The aorta showed a marked atherosclerosis, and the coronary arteries revealed a moderate to marked arteriosclerosis. Microscopic examina-

* Resident, Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

tion of the myocardium revealed diffuse atrophy of the myocardial fibers and interstitial fibrosis (Fig. 1). Fibrosis of the conduction system was probably responsible for the arrhythmia.

The lungs were voluminous and rigid. The alveoli were overdistended, and in some areas the alveolar septa were broken. The large pulmonary arteries were dilated and atherosclerotic. The parenchyma of the lung showed evidence of chronic passive congestion. An elastic tissue stain demonstrated ruptured alveolar septa and proliferation, and thickening of the elastica of the septa.

The liver was firm but normal in weight. The surface of the liver was granular and revealed many fine linear scars. The hepatic veins were dilated secondary to chronic passive congestion. A connective tissue stain illustrated the distortion of the parenchyma by fibrous septa. The septa extended from the central veins and connections from central vein to central vein, and also portal tracts reflected an early cardiac cirrhosis (Fig. 2).

The spleen was greatly enlarged. Fibrotic or hyalinized plaques on the surface suggested a perisplenitis. The pulp was cellular and showed marked reticuloendothelial hyperplasia, congestion of the red pulp, and diminution of the Malpighian bodies.

The kidneys were sclerotic. They were slightly decreased in weight, and finely nodular due to hypertrophy of the nephrons. The tubules were atrophic and filled with a proteinaceous material. In addition, the kidneys contained multiple large cortical adenomas.

Throughout the jejunum and ileum were multiple mucosed nodules of varying size, some extended to the serosa (Fig. 3). These were composed of retic-

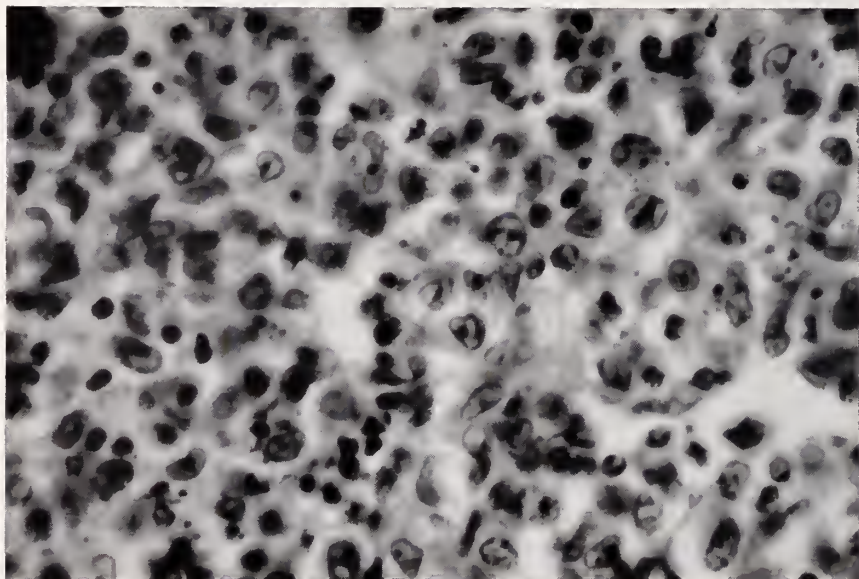


FIG. 4. Diffuse lymphomatous infiltration of the mucosa of the small bowel (H & E $\times 400$).

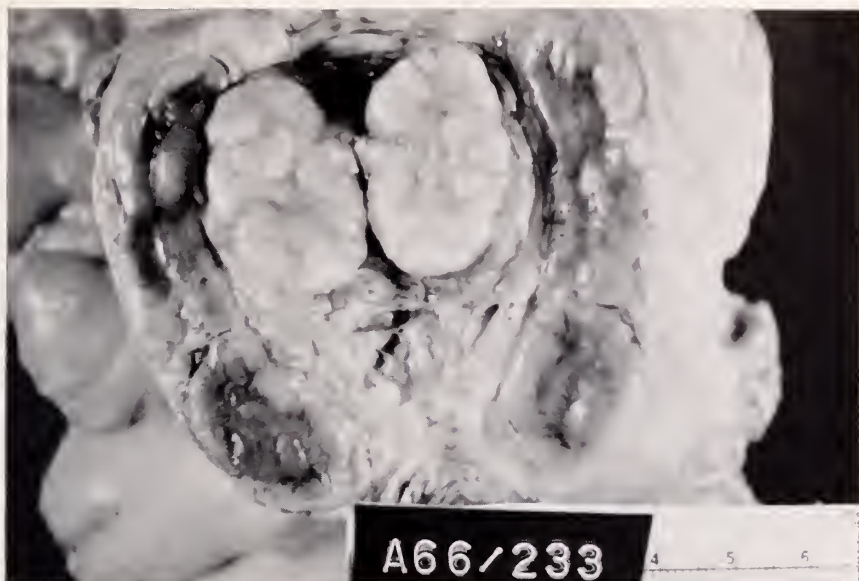


FIG. 5. Hyperplastic lymph nodes surrounding a lymphomatous node in the mesentery.



FIG. 6. Complete effacement of follicular architecture of a mesenteric lymph node by reticulum cells (H & S $\times 40$).

ulum cells, and some showed ulcerations into the mucosa, submucosa, and muscularis (Fig. 4). The intestinal bleeding originated from one of these nodules.

The nodes of the mesentery were hyperplastic, fish-flesh in appearance, and

soft (Fig. 5). The follicular architecture of the lymph nodes was completely effaced by large, atypical reticulum cells (Fig. 6).

The bone marrow was also hyperplastic, but did not contain malignant cells. Megakaryocytes were adequate.

In summary, the gastrointestinal bleeding was due to a reticulum cell sarcoma which involved the ileum and jejunum, and mesenteric lymph nodes.

Question: What do you think was the cause of the heart disease?

Dr. Feinberg: The patient had hypertension and calcific aortic stenosis.

Question: Was the diagnosis made at the time of exploration?

Dr. Feinberg: The biopsy obtained at surgery showed only ulcerations of the small intestines. Reticulum cells were not apparent.

Final Diagnoses:

1. LYMPHOSARCOMA, RETICULUM CELL TYPE, INVOLVING JEJUNUM, ILEUM AND MESENTERIC LYMPH NODES.
2. HYPERTENSIVE AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE.
3. CARDIAC CIRRHOSIS.

References

1. Gregg, J. A., Herkovic, T., and Bartholomew, L. G.: Ascites in Systemic Amyloidosis, *Arch Int Med* 116:605, 1965.
2. Kapp, J. P.: Gastrointestinal Hemorrhage and Protein Loss in Primary Amyloidosis, *Gut* 6:14, 1965.
3. Steig, J.: Hepatic Amyloidosis with Portal Hypertension, *JAMA* 191:497, 1965.

Received for publication January 15, 1969

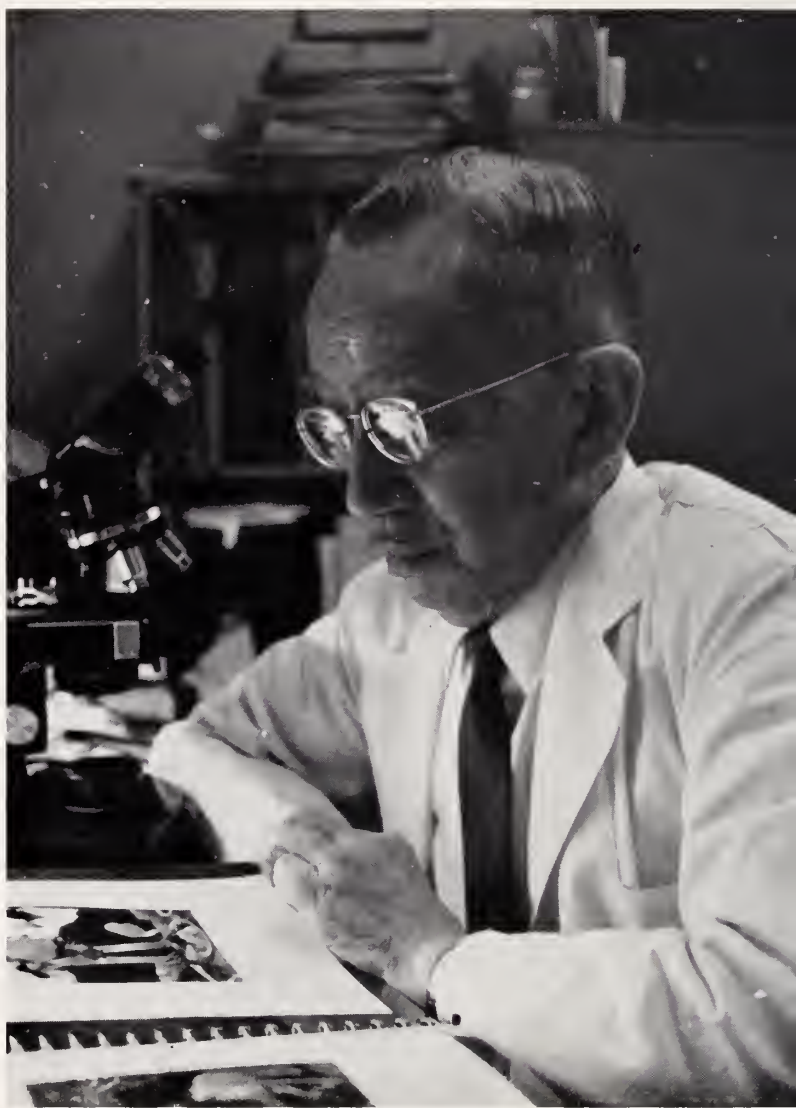
In Memoriam

SADAO OTANI, M.D.

1892-1969

On March 7, 1969 the Mount Sinai School of Medicine and Hospital lost one of its giants. Dr. Otani was born on December 24, 1892 in Japan. He graduated from the Chiba Medical School, Japan, in 1918. For the next three years, he was Assistant in Pathology at the Chiba Medical School. A one-year internship in the Red Cross Hospital, Japan, followed. For the next two years, Dr. Otani took graduate training in Germany. In January 1925 he became Research Assistant in Pathology at the New York Post-Graduate Medical School and Hospital. In May 1927 he became Assistant Pathologist at The Mount Sinai Hospital, and in 1937, Associate Pathologist. In 1947 Dr. Otani was appointed Assistant Clinical Professor of Pathology at Columbia University, and in 1949, Associate Clinical Professor. In 1953 he was appointed Attending Pathologist of The Mount Sinai Hospital and Associate Director of the Department of Pathology. In 1965 he was appointed Professor of Pathology of the Mount Sinai School of Medicine. He was a member of the American Association of Pathologists and Bacteriologists (1928), the New York Pathological Society (1929), the Harvey Society of New York (1951), and an honorary member of the Japanese Pathological Society and the Colombian Pathological Society. He was appointed Consultant for the Tumor Registry of the American Society of Clinical Pathologists (1944), and was Vice President of the New York Pathological Society (1949). Dr. Otani published scientific papers on periarteritis nodosa, structural details of the islands of Langerhans of the pancreas, the finer anatomy of the vascular channels of the spleen, pancreatitis, on malignant nephrosclerosis, solitary or eosinophilic granuloma of bone, ulcerative colitis, regional enteritis, and regional enterocolitis. The paper on malignant nephrosclerosis published in 1931, co-authored with Dr. Paul Klemperer, is considered a classic and definitive paper on this subject. The paper on solitary granuloma of bone, co-authored with Dr. Joseph Ehrlich, was the first description of this lesion. The name of Dr. Otani is also associated with the glomus jugulare tumor described in publications from this hospital. He was the first to recognize the true pathological nature of this neoplasm.

The facts noted above cannot possibly do justice to the life of Dr. Otani. His coming to The Mount Sinai Hospital with Dr. Klemperer in 1927 marked the beginning of an era in the history of the hospital. The team of Klemperer and Otani formed the secure foundation for the extraordinary achievements of the Hospital staff. For more than forty years, Dr.



SADAO OTANI, M.D.
1892-1969

Otani was consultant par excellence for all surgical-pathological problems. His knowledge, based on years of experience, a fantastic memory, and extraordinary medical judgment, was invaluable to innumerable physicians who came from far and wide to secure his opinion. Countless thousands of people owe much of their clinical care to him. They are totally unaware of this, and this is exactly the way Dr. Otani wanted it. He taught that the role of the pathologist was clinical; it was his duty to understand the life history of disease based on critical evaluation of the literature backed by personal observations, in order that suitable therapy would be administered and the correct prognosis made. During his many years of totally dedicated service, he was a vital part of the training of hundreds of pathologists. The Pathologists Alumni Association of The Mount Sinai Hospital is a testimony to Dr. Klemperer and Dr. Otani. For many years, Dr. Otani conducted post-graduate courses in pathology as well as numerous clinical-pathological conferences with such crystal-clear clarity and enthusiasm, that every session was an unforgettable learning experience. When color photography was introduced, he pioneered its development in our institution. Slides replaced the carefully dissected and mounted specimens which Dr. Otani spent so many hours collecting. Originally, and for some time, he did his own characteristically careful and beautiful color development. He designed the light boxes used for photography of specimens as well as special homemade viewing equipment that made it possible for physicians who consulted him to see microscopic slides with him. Dr. Otani was a technical perfectionist, and trained technicians to attain his high standards. He was a fanatic Giants fan (as long as the team remained in New York), and a devotee of the Japanese game of Go.

Dr. Otani was an extraordinarily shy man. It took time before one realized the intensity of his feelings and his deep and abiding love for his fellow man, his fellow physician, his medical specialty, and his hospital. He had a deep distrust and deep dislike for any taint of intellectual dishonesty, which he was quick to detect. On the other hand, he was equally quick to recognize substance in people, papers, or projects. As a result, he generated a deep emotional commitment in all who touched him, which explains the void that all his friends feel. To his intimates, it was abundantly clear that he was bursting with pride and love of his family. We extend our deepest sympathy to his wife, Isako, to his daughters, Michiko, Hiroko and Emy, and to his grandchildren, Robin and Paul Weller. His happiest moments were spent with you.

BERNARD S. WOLF, M.D.
for the
EDITORIAL BOARD

Selected Experiences with Cardiac Pacing*

PHILIP SAMET, M.D. AND JOHN W. LISTER, M.D.

The development and clinical utilization of three modes of cardiac pacing (1-10)—fixed rate, demand, and P wave synchronous, has resulted in a wide variety of interesting and unusual electrocardiographic patterns associated with the use of these pacing techniques. The purpose of this paper is to illustrate some of these patterns. In addition to these different pacing methods, different cardiac chambers may be utilized as pacing sites. These include the two atria and the two ventricles.

Atrial pacing is generally performed by the pervenous endocardial route. Ventricular pacing is performed by the endocardial or by the epicardial route. The three commonly used pacing methods therefore include:

- 1) Atrial temporary pacing: endocardial
- 2) Ventricular temporary pacing: endocardial
- 3) Ventricular permanent pacing:
 - (a) epicardial
 - (b) endocardial

Temporary pervenous endocardial right atrial pacing in turn is performed for varied indications:

- 1) Pacing for slow ventricular rates
 - (a) fixed rate pacing
 - (b) demand pacing of the QRS blocking variety
- 2) Pacing for rapid ventricular rates
 - (a) paired pacing
 - (b) coupled pacing
 - (c) rapid atrial stimulation
 1. for supraventricular arrhythmias
 2. for ventricular arrhythmias
 - (d) atrial stimulation at near physiologic rates

Permanent pervenous endocardial and permanent epicardial atrial pacing have been utilized only on rare occasions for cardiac pacing (1, 2). Its ultimate role in cardiac pacing is yet to be determined.

Temporary ventricular pacing is done by the pervenous endocardial route:

- 1) Pacing for slow ventricular rates
 - (a) fixed rate pacing
 - (b) demand pacing of the QRS blocking variety
 - (c) synchronous P wave pacing
- 2) Pacing for rapid ventricular rates
 - (a) paired pacing

From the Division of Cardiology, Department of Internal Medicine, Mount Sinai Hospital, Miami Beach, Florida.

* Presented as the Lilienthal Lecture at the Mount Sinai School of Medicine, New York, N.Y., on January 18, 1969.

- (b) coupled pacing
- (c) ventricular pacing

Permanent ventricular pacing has been carried out by pervenous endocardial and by the epicardial routes:

- 1) Pacing for slow ventricular rates: epicardial
 - (a) fixed rate pacing
 - (b) synchronous P wave pacing
 - (c) demand pacing
 - 1. QRS blocking
 - 2. QRS synchronous
- 2) Pacing for slow ventricular rates: endocardial
 - (a) fixed rate pacing
 - (b) synchronous P wave pacing
 - (c) demand pacing
 - 1. QRS blocking
 - 2. QRS synchronous

Permanent ventricular pacing by either the endocardial or epicardial technique has also been utilized for the therapy of rapid ventricular rates, although experience in this area is as yet limited.

Atrial Pacing

Right atrial pacing for sinus bradycardia is illustrated in Figure 1. The control R-R interval varies from 1.20 to 1.25 seconds. The atrial stimulus pacing interval is decreased to 0.75 seconds. Each stimulus is followed by a P wave, in turn followed by a QRS complex identical in form and duration to the control QRS complex. The use of right atrial fixed rate pacing to control severe sinus bradycardia with runs of ventricular premature beats in acute myocardial infarction is illustrated in Figure 2. In the upper strip, a run of ventricular tachycardia complicates sinus bradycardia. Nylocaine infusion at 1.5 mg/min is associated with severe bradycardia. Atrial pacing readily eliminates both the sinus bradycardia and the ventricular premature beats.

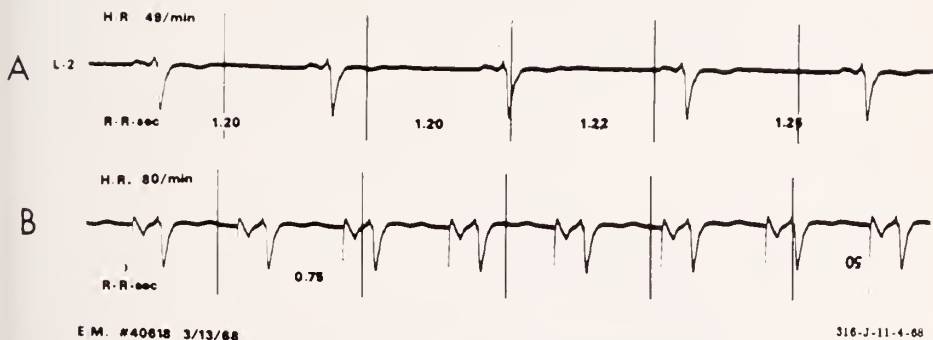
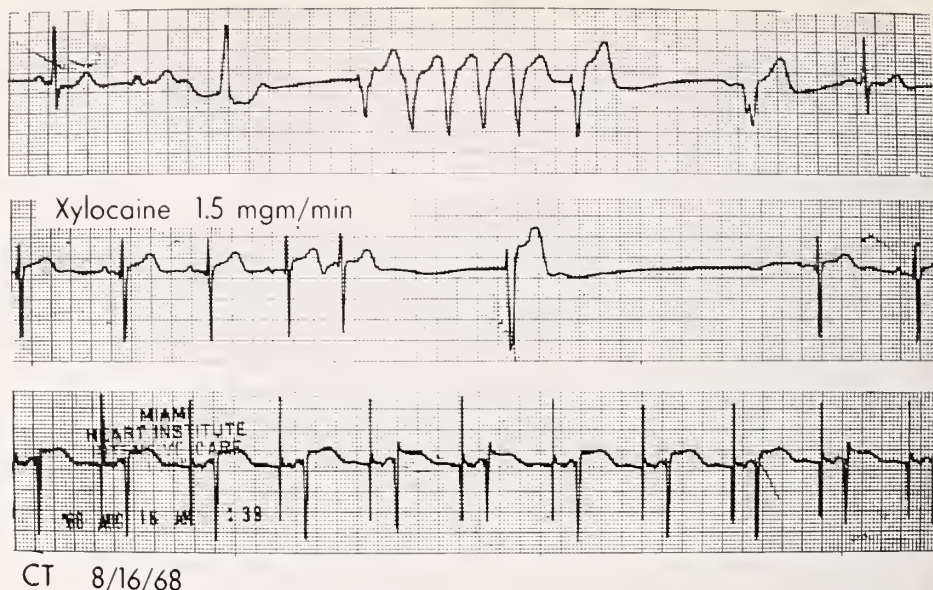


FIG. 1. Sinus bradycardia upper strip. Time lines at one second intervals. Lower strip illustrates atrial pacing.



CT 8/16/68

FIG. 2. Sinus bradycardia with runs of ventricular tachycardia in a patient with acute myocardial infarction. Xylocaine infusion resulted in further slowing of the ventricular rate. Atrial pacing permitted maintenance of an adequate heart rate.

Bradycardia with nodal rhythm may be treated in a similar fashion (Fig. 3). In strip A, from above down, are shown the simultaneously recorded atrial unipolar lead (AUE), atrial bipolar lead (ABE), a second unipolar lead, and standard lead 2. The retrograde P wave follows the QRS complex. In strip B, the same four leads are illustrated during atrial pacing, with increase in the ventricular rate.

Atrial pacing may, however, have intrinsic problems, especially in the presence of atrioventricular junction disease (Figs. 4 and 5). In Figure 4, upper strip, sinus bradycardia, rate 52/min is present. After exercise, the atrial rate rises to 62 but the ventricular rate falls to about 31/min with 2:1 atrioventricular block. The application of carotid sinus pressure slows the atrial rate, but the ventricular rate rises with restoration of 1:1 conduction. The problem of disease at the A-V junction is further illustrated in Figure 5. In lead 1, 5:30 PM, October 8, 1968, 2:1 A-V block and 1:1 conduction are both present. 2:1 conduction is present in the second strip, 3:20 AM, October 9, 1968; at 12:00 AM, October 10, 1968 and 2:20 AM, October 10, 1968, 1:1 conduction with sinus tachycardia are noted. At 3:30 AM, October 10, 1968, atrial flutter with a high degree of A-V block and a slow ventricular rate were observed. A long period of ventricular asystole followed at 4:10 AM, October 10, 1968. Isoproterenol infusion (last strip, Fig. 5) transiently increased the ventricular rate, but a right ventricular pacing catheter was ultimately required. The last two figures illustrate the fact that in the presence of A-V junction disease, an increase in atrial rate may be associated with a decrease in the ventricular rate.

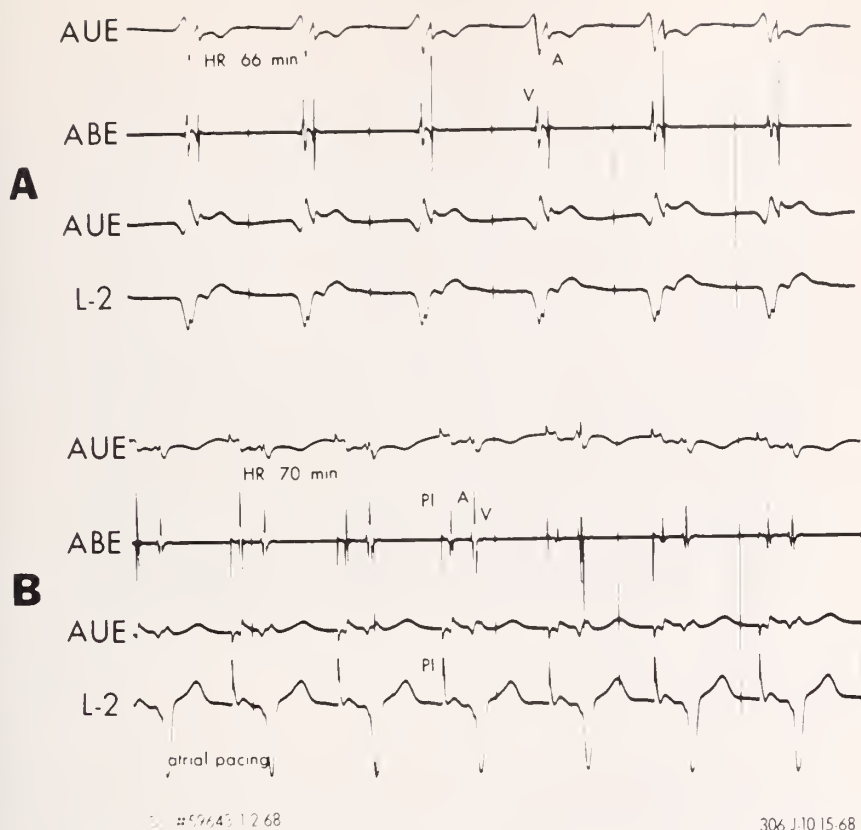


FIG. 3. Bradycardia and nodal rhythm; treatment with atrial pacing. Strip A, from above down: right atrial unipolar lead, right atrial bipolar lead, right atrial unipolar lead, and lead 2. The QRS complex precedes the P wave. Time lines at 1 sec intervals. Strip B: during atrial pacing. P.I. refers to pacemaker impulse, "A" to the atrial complex, and "V" to the ventricular complex.

Under special circumstances, advantage may be taken of the physiologic properties of the atrioventricular junction. When the atrial rate is increased by atrial pacing, prolongation of the P-R interval occurs even in normal subjects. Eventually, at rates of 150–180/min, second degree atrioventricular block occurs even in normal subjects, and not all P waves are followed by QRS complexes. The latter approach may be utilized in the therapy of supraventricular tachycardias (Figs. 6–9). In the application of the techniques of rapid atrial stimulation, stimuli are applied to the right atrial wall at a rapid rate (11). In Figure 6, atrial flutter with 2:1 block is present, upper strip. The flutter waves are more evident after carotid sinus pressure (CS), lead 2. AUE refers to the right atrial unipolar lead which revealed atrial flutter, rate 300. A Medtronic paired pulse pacer is then employed to apply right atrial stimuli at a rate of 540/min. The ventricular rate is slowed. When the rapid atrial stimulation is stopped, transient sinus rhythm appears, to be followed by recurrent supraventricular tachycardia. Digitalis therapy

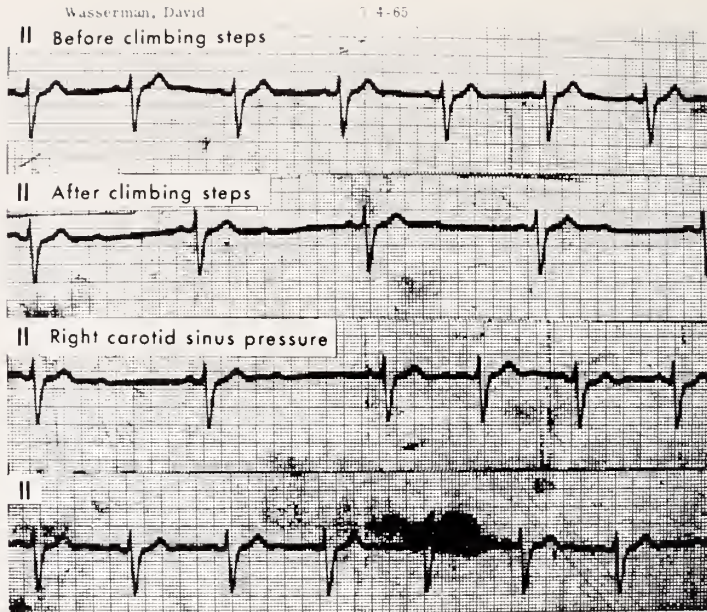


FIG. 4. Patient with sinus bradycardia, rate 52. During exercise the atrial rate rises to 62 but the ventricular rate falls to 31 with 2:1 atrioventricular block. Carotid sinus stimulation decreases the atrial rate but increases the ventricular rate.

was then given. One week later, as seen in Figure 7, reapplication of rapid atrial stimulation is followed by transient atrial fibrillation. Ten minutes later, sinus rhythm returned. Conversion of a supraventricular tachycardia to normal sinus rhythm 14 seconds after rapid atrial stimulation is shown in Figure 8. Atrial stimulation may result in atrial fibrillation, Figure 9, with alteration of atrial flutter to atrial fibrillation with a decrease in ventricular rate. Increase in the atrial rate during atrial stimulation results in ventricular slowing.

We have utilized rapid atrial stimulation in more than 30 cases; a potential complication has been observed in only one patient (Figs. 10-12). Atrial flutter was converted to atrial fibrillation by rapid atrial stimulation (Fig. 10). Seventy seconds later, as seen in Figure 11, cardiac standstill developed with a slow nodal rhythm for about ten seconds. This experience has emphasized the necessity for facilities for cardiac pacing when using rapid atrial stimulation. Demand atrial or ventricular pacing may be utilized if cardiac standstill develops (Fig. 12).

Atrial pacing may also be of use in study of the atrioventricular conduction system (Figs. 13 and 14). A unipolar atrial lead, a bipolar atrial lead, and lead 2 are shown in Figure 13. "A" refers to the atrial complex, "BH" the HIS bundle electrogram, and "V" the ventricular electrogram. These records are made by a close bipolar electrode catheter passed into the right atrium with a tip position at the tricuspid valve. The interval between the A and HB

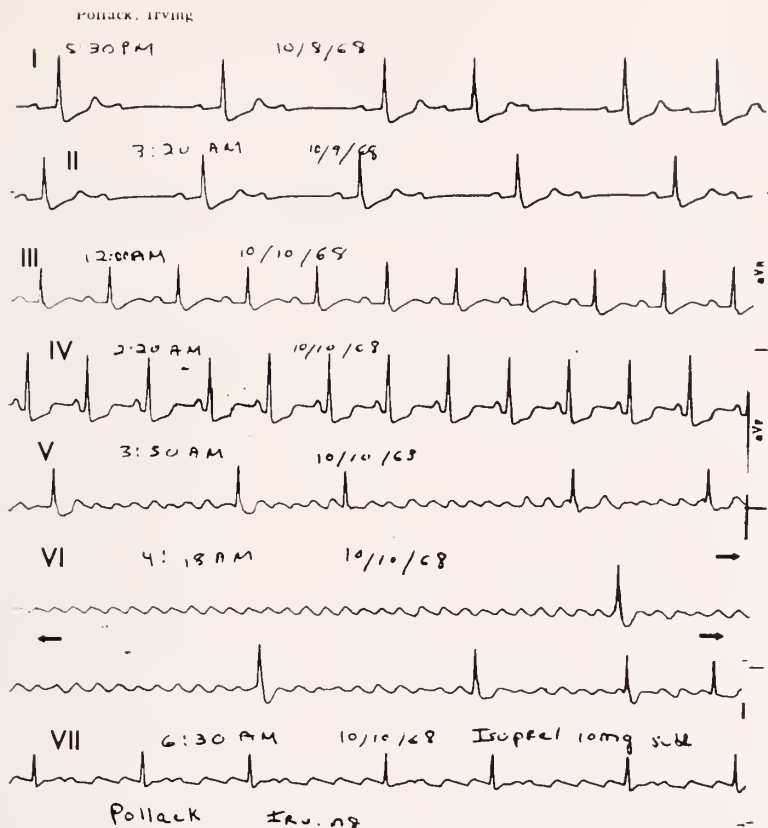
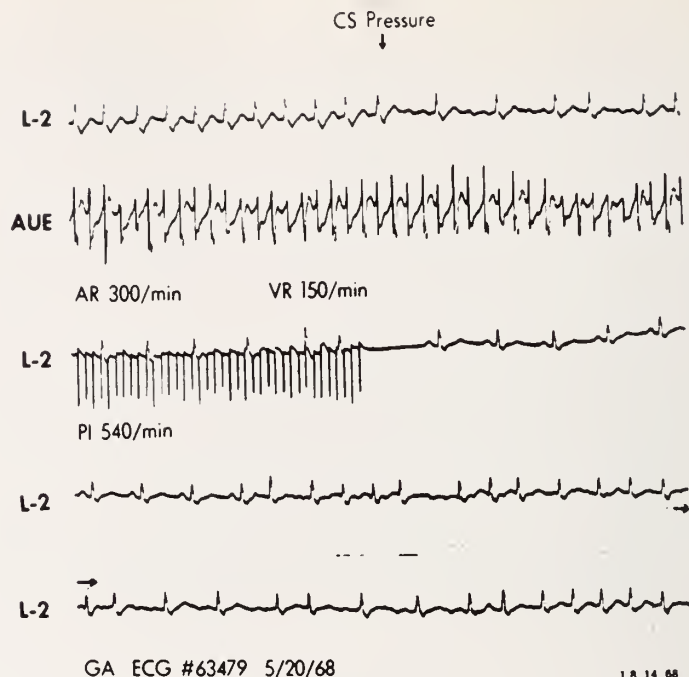


FIG. 5. Atrioventricular junctional disease (see text for details).

complexes is the AH time; that between the BH and V complexes is the HV time (upper limit 35–50 m sec). These latter two parameters plus the P-A (P wave to “A” complex onset) make up the P-R interval of the clinical electrocardiogram. The introduction of pacer impulses (PI) via a right atrial pacing catheter, simulating atrial premature beats, permits analysis of A-V conduction. As the P-P interval is altered, changes in A-H and H-V times may occur, as may changes in the QRS complex. Atrioventricular block between the atrium and HIS bundle or between the HIS bundle and the ventricular electrogram may be observed in Figure 14, section B.

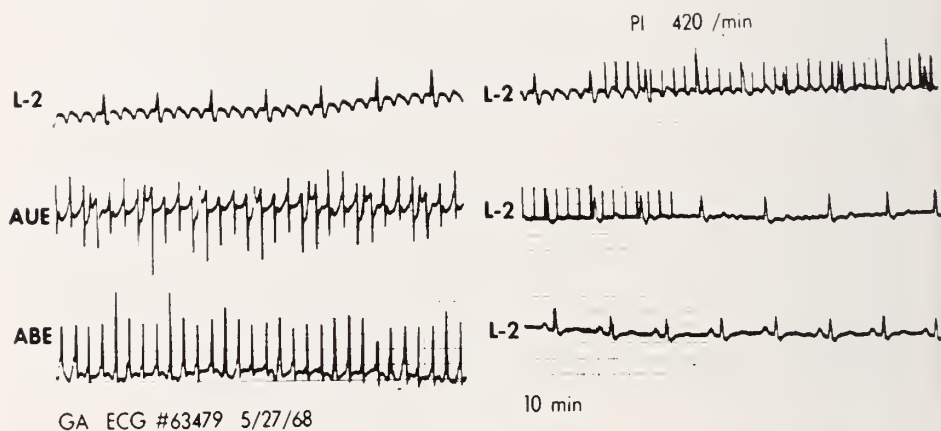
Ventricular Pacing

The original form of ventricular pacing clinically utilized is fixed rate pacing (Fig. 15). Stimuli are delivered to the ventricle at a constant rate regardless of the underlying rhythm, i.e., heart block or conducted beats. If spontaneous ventricular premature beats occur, the stimuli may occur in the area of the so-called vulnerable phase, the obvious disadvantage of



J 8 14 68

Fig. 6. Rapid atrial stimulation for treatment of supraventricular tachycardias (see text).



J 8 14 68

Fig. 7. Digitalis and rapid atrial stimulation for treatment of supraventricular rhythms (see text).

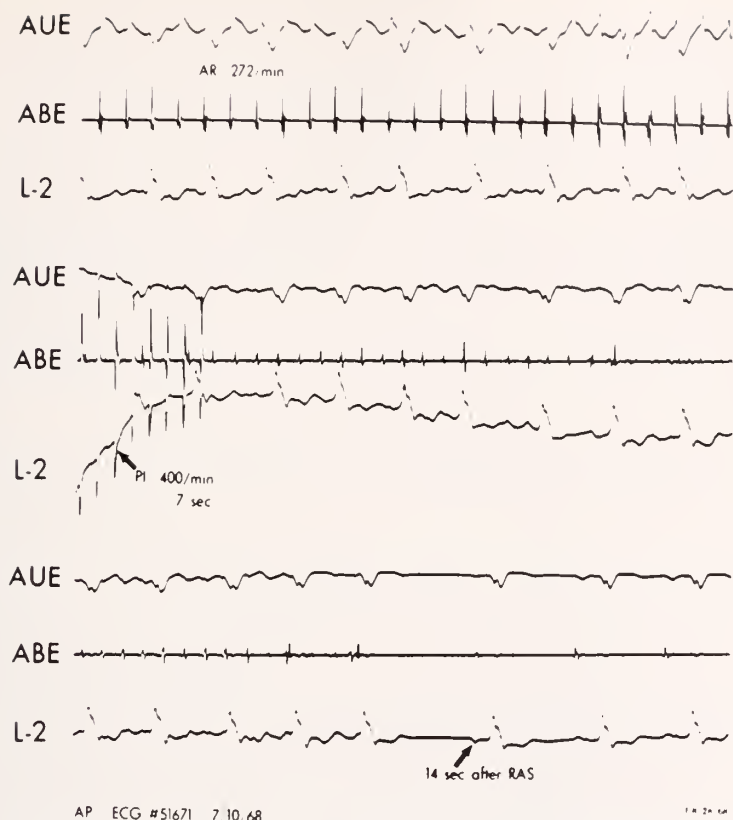


Fig. 8. Conversion to normal sinus rhythm 14 seconds after rapid atrial stimulation (see text).

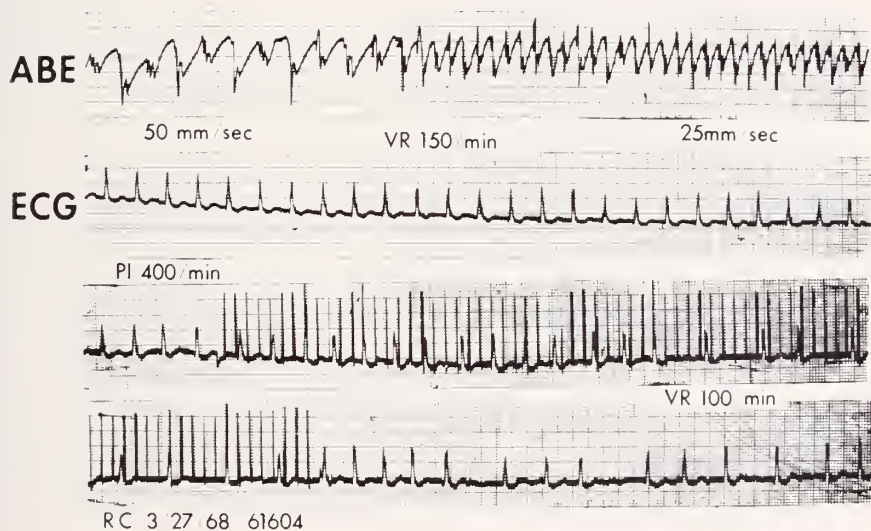


Fig. 9. Persistence of atrial fibrillation after rapid atrial stimulation (see text).

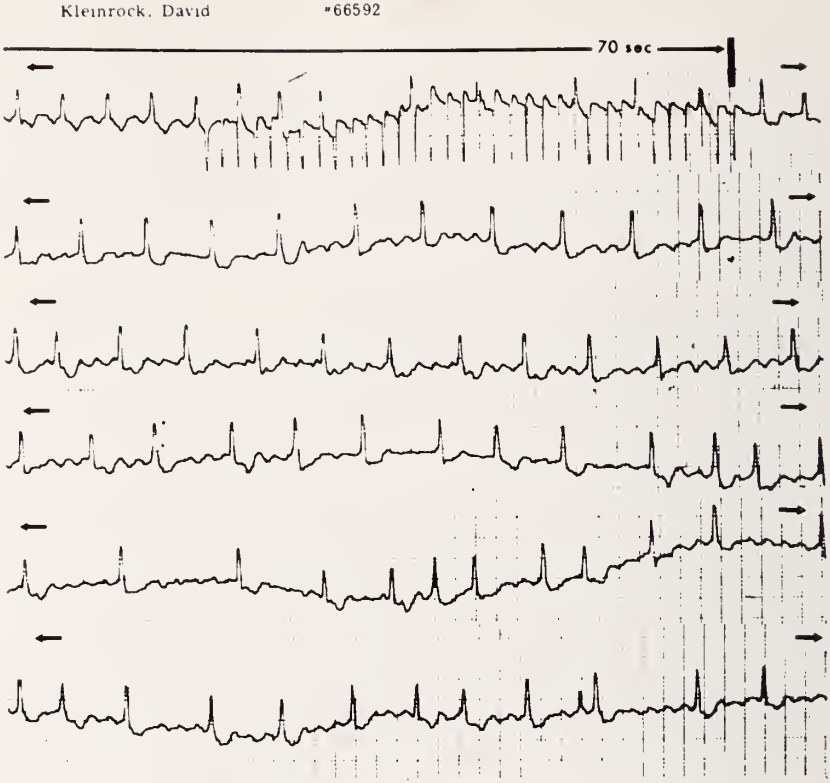


FIG. 10. Conversion of atrial flutter to atrial fibrillation (see text).

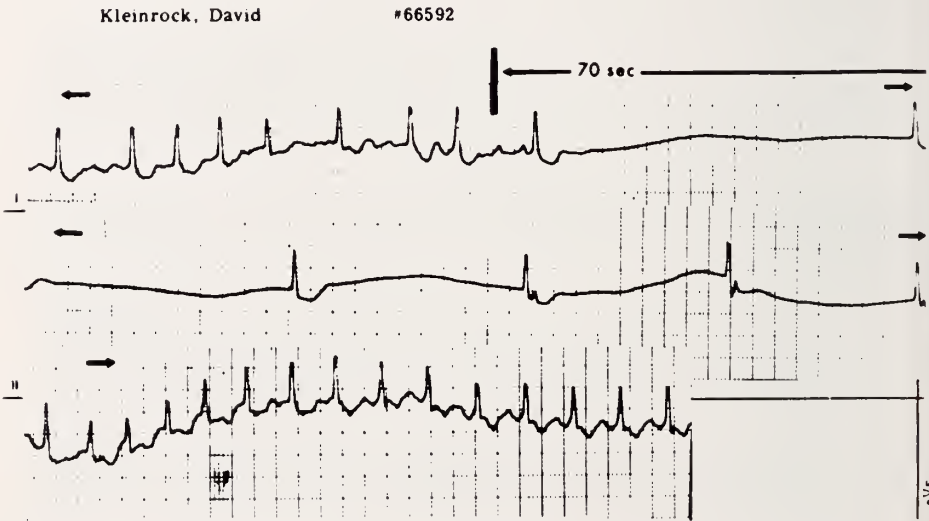


FIG. 11. Cardiac standstill 70 seconds later, same patient as in Fig. 10 (see text).

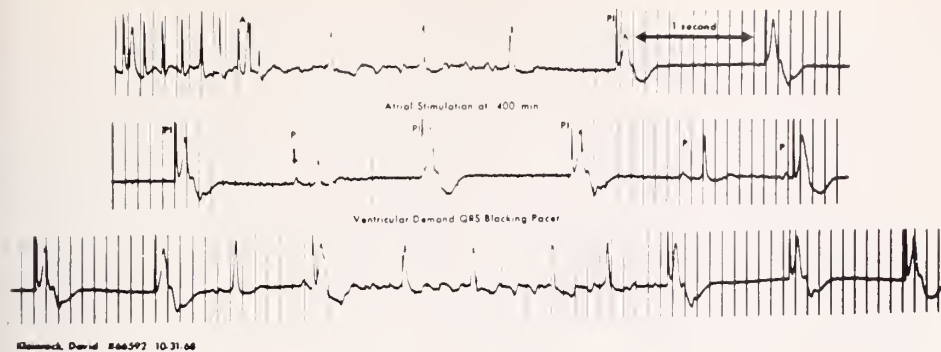
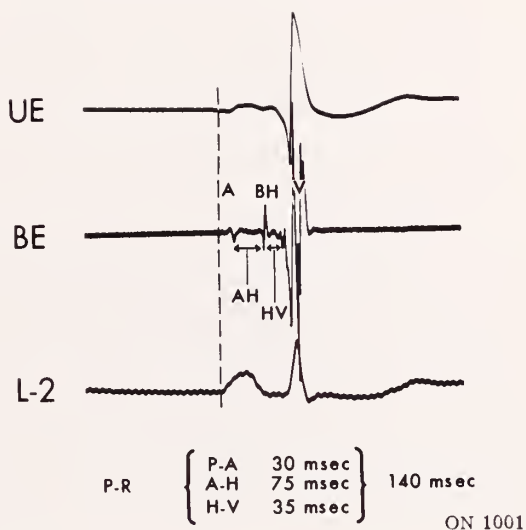


Fig. 12. Cardiac pacing after rapid atrial stimulation (see text).

FIG. 13. HIS bundle recording. The unipolar and bipolar right atrial leads are recorded simultaneously with lead 2. "A" refers to the atrial complex, "BH" to the HIS Bundle, and "V" to the ventricular complexes. AH is the time from onset of the atrial to HIS Bundle complex; H-V is the Bundle of HIS to ventricular activation time; P-A refers to the interval from onset of the P wave in lead 2 to the atrial deflection. The vertical line marks the onset of the P wave in lead 2.



fixed rate pacing. The second variety of ventricular pacing that has been employed clinically, is the P wave synchronous mode of pacing, in which the ventricular pacing rate follows the sinus rate up to a maximum rate of about 125, due to a built-in refractory period of approximately 480 msec (Fig. 16). Each P wave is followed by a pacer stimulus and a paced ventricular beat. If the atrial rate exceeds 125, 2:1 block occurs; if the atrial rate exceeds 250, 3:1 block occurs, as in Figure 17, in which every third flutter wave is detected and followed by a pacer stimulus and a QRS complex. The third variety of ventricular pacing is the demand or standby pacer. As originally conceived, a pacer stimulus appeared only if the intrinsic ventricular rate fell below the pacer rate. Thus, if the pacer rate is set at 60/min, a pacer

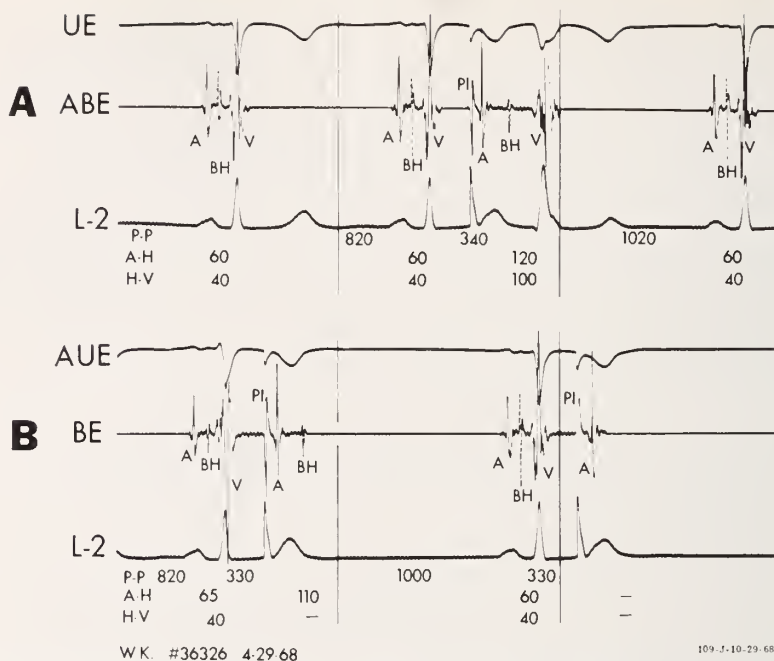


FIG. 14. Use of single premature right atrial pacing stimuli to study atrioventricular conduction (see text).

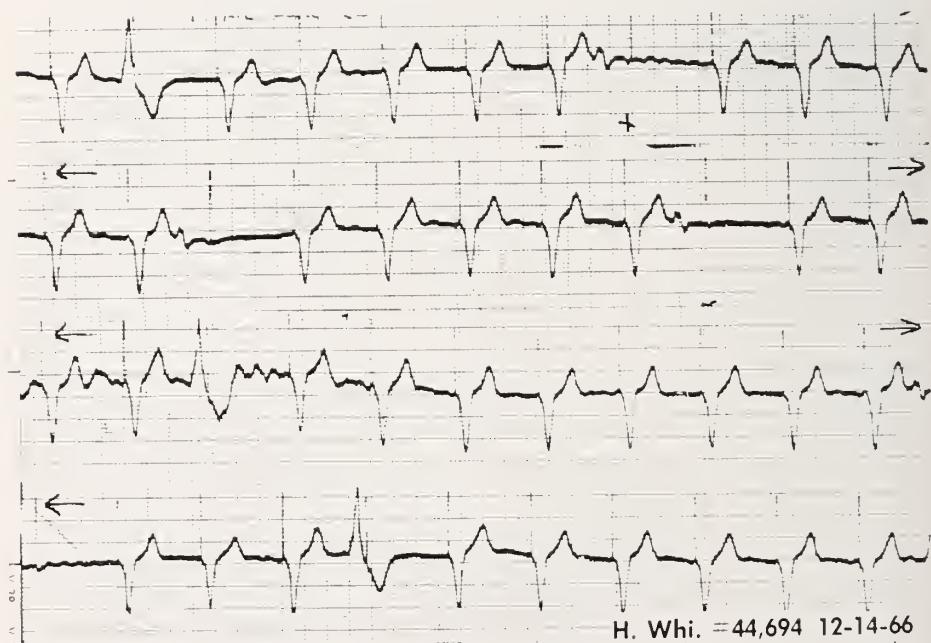


FIG. 15. Fixed rate right ventricular pacing. The stimuli fall at a constant rate (see text).

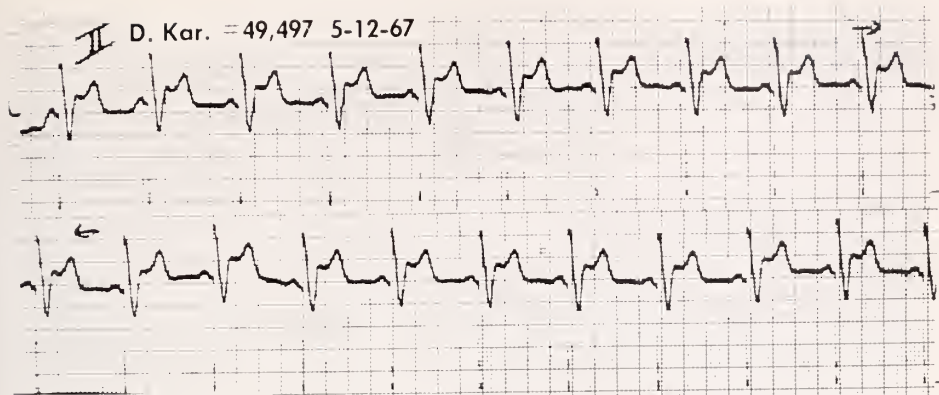


FIG. 16. P wave synchronous pacing with the Atricor pacer (see text).

stimulus appears if the spontaneous R-R interval exceeds 1 second; if the rate is set at 120/min, a pacer stimulus appears if the spontaneous R-R interval exceeds 0.5 seconds; if the rate is set at 30/min, a pacer stimulus appears if the spontaneous R-R interval is more than 2 seconds. This variety of demand pacer is the QRS blocking demand pacer; the pacer stimulus is blocked and does not appear if the spontaneous heart rate is faster than the pacer rate (Fig. 18). In the later figure, normally conducted beats are present in the first and third strip. Only paced beats are seen in the middle strip. The third and eighth beats in the first strip are true fusion beats, i.e., conducted beats occur via the normal pathway plus the stimulus initiated pathway. The seventh beat of the first strip is a conducted beat in which the QRS is deformed by the stimulus artefact. The second variety of demand pacer is the QRS synchronous pacer, a demand pacer in which paced beats occur if the spontaneous rate falls below the present demand rate; on the other hand, if spontaneously conducted beats occur, the stimulus artefact is not absent, but distorts the QRS complex (Fig. 19). During conducted beats (beats No. 2, 5, 6, 8 and 9, strip one) the initial portion of the QRS complex is the spontaneous beat which is deformed by the pacer stimulus. If a paced beat is present, the initial portion of the QRS is the pacer stimulus itself (complexes 1, 3, 4, 7 and 10, strip one).

The two varieties of demand pacer each have advantages and disadvantages. The principal disadvantage of the Ektacor QRS synchronous demand pacer is the necessity for a refractory period to keep the maximum rate at 150 with a refractory period of 400 m sec, and 120 with a refractory period of 500 m sec. In addition, the pacer produces stimuli at all times, with either conducted or spontaneous beats, and therefore the life of the unit is probably less than that of the QRS blocking pacemaker. However, there is a potential problem with the latter type of demand pacer. External stimuli may produce patterns falsely interpreted as QRS complexes, thus inactivating the pacer even in the absence of spontaneous QRS complexes (Fig. 20). In the initial portion of the

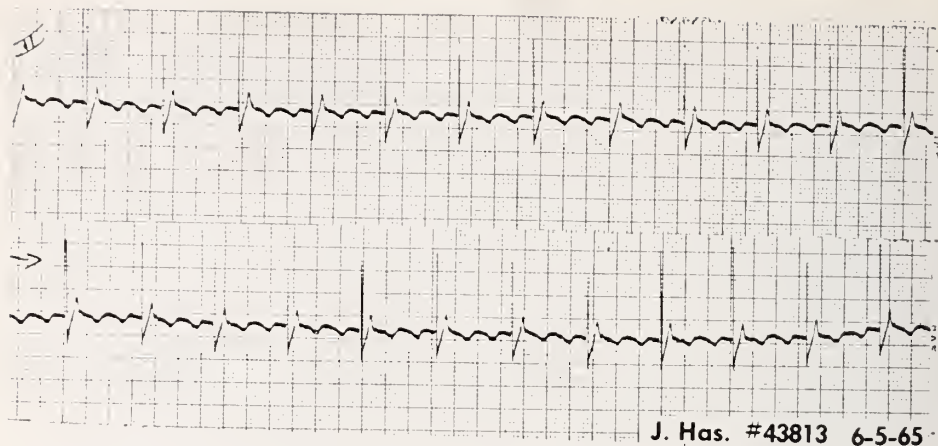


Fig. 17. Atrial flutter with 3:1 pacer block in a patient with complete heart block (see text).

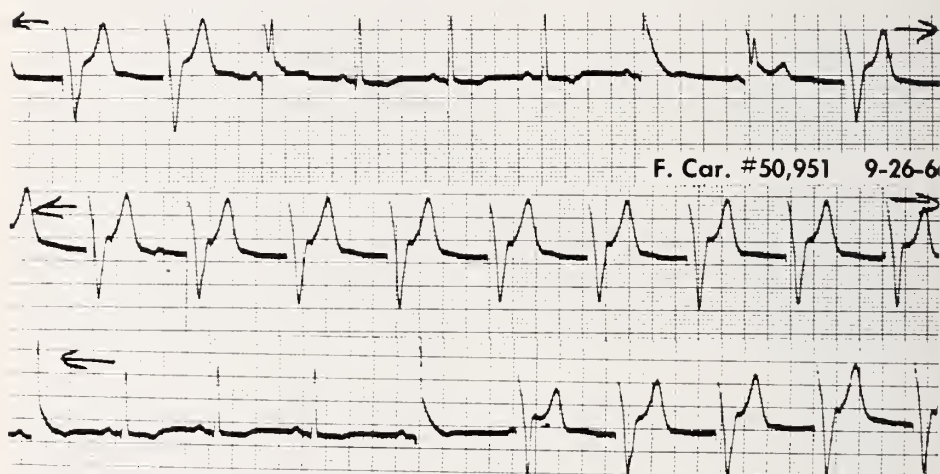


Fig. 18. QRS blocking demand pacer (see text).

upper strip, the first two beats are conducted. The third and fourth beats are conducted; the downward stimulus artefact is ineffective in beats three and four. Carotid sinus pressure is applied (black line above ECG) midway through the first strip, slowing the spontaneous ventricular rate so that demand pacing is the dominant mode. At the end of strip one and continuing through the first half of strip two, upright stimuli are applied at a rapid rate to the anterior chest wall via a second Medtronic pacer and two electrodes. These upright stimuli are interpreted as QRS complexes by the permanent pervenous Medtronic QRS blocking demand pacer. The latter is then inoperative for the entire period of chest wall stimuli, so that the

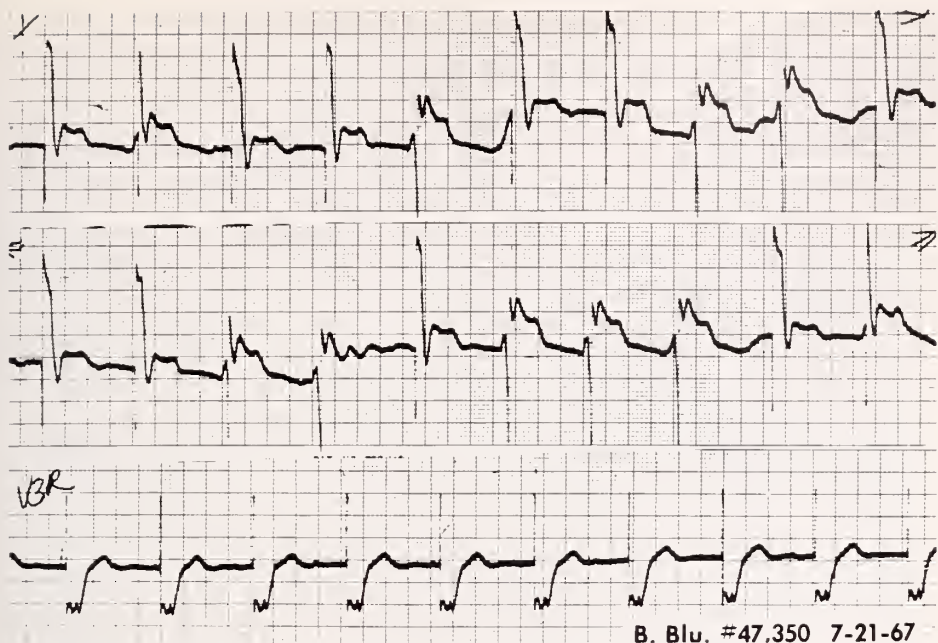


FIG. 19. QRS synchronous demand pacer. The pacer stimulus appears with all complexes, before the QRS complex in paced beats and during the QRS complex in conducted beats (see text).

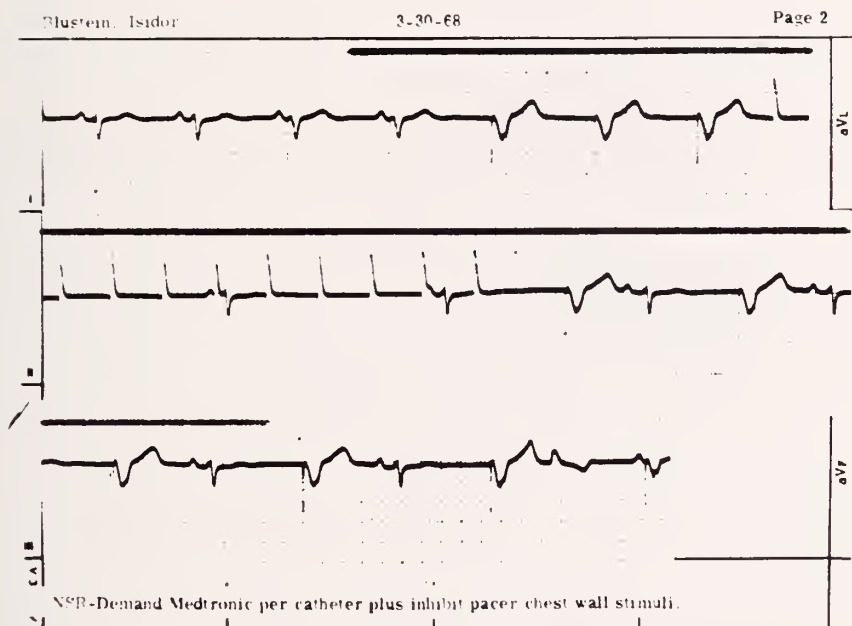


FIG. 20. Inactivation of the permanent Medtronic percutaneous QRS blocking demand pacer by chest wall electrical stimuli. The ventricular rate falls to less than 30 at this time (see text).

THELMA SMITH IMPLANTED EKTORCOR

3-25

Bipolar Atrial Pacing with Medtronic External Pacer

Medtronic Pacer rate and Ektocor rate 113



FIG. 21. Ektocor QRS synchronous demand pacer. Response to right atrial pacing stimuli at 113/min. 1:1 response is seen (see text).

Smith, Thelma

3-26-68

Rate 200

Page 4

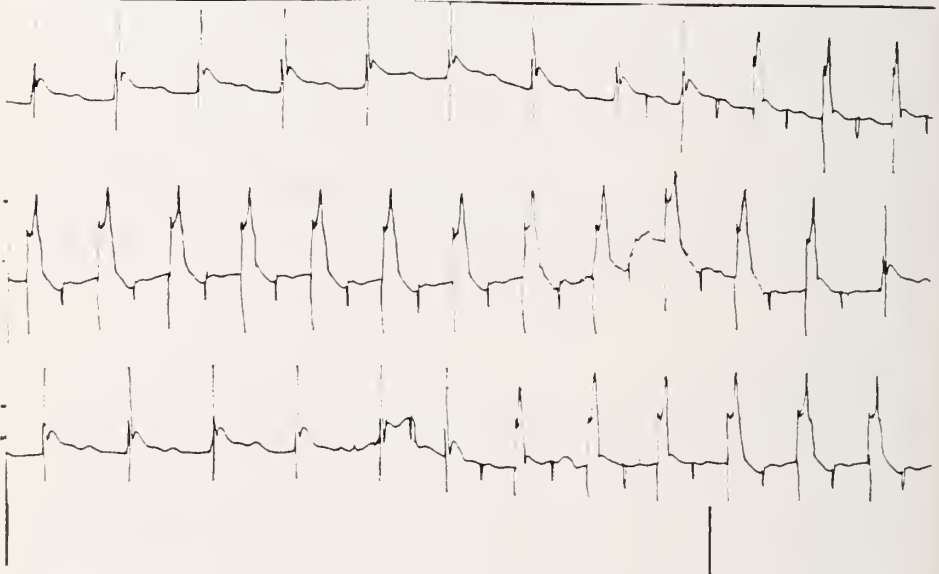


FIG. 22. 2:1 Ektocor pacer response during right atrial pacing, stimuli at a rate of 200. Same patient as Fig. 21 (see text).

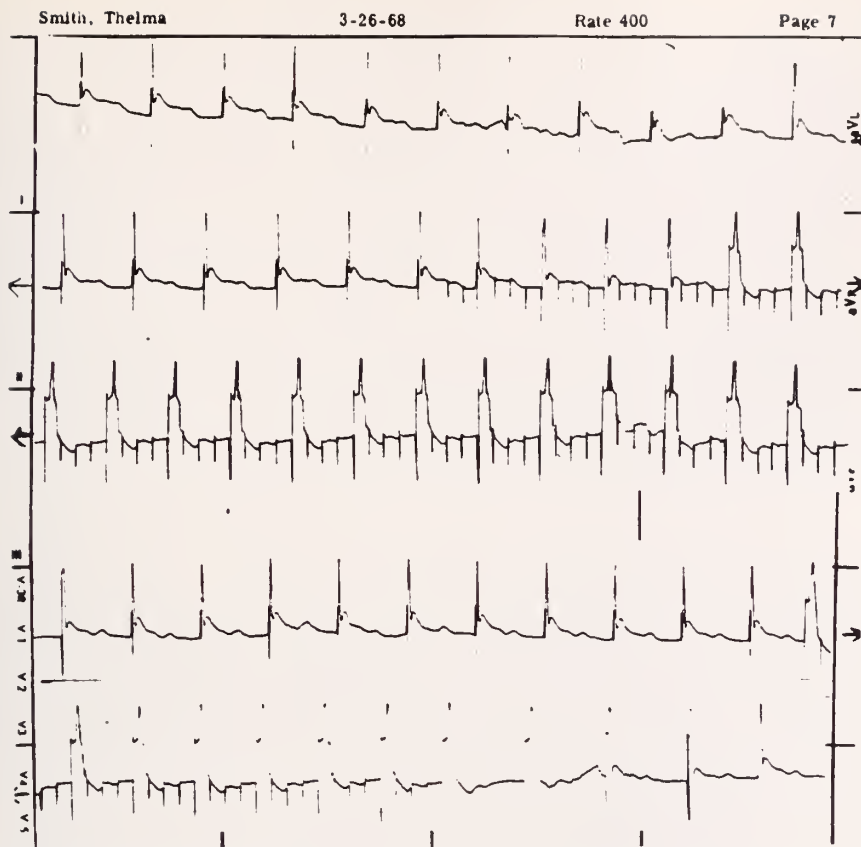


FIG. 23. Intermittent atrial pacing at 400, with 4:1 Ektacor pacer block (see text). Same patient as in Figs. 21 and 22.

ventricular rate (first two QRS complexes in strip two) becomes quite slow. Carotid sinus pressure is released in the third strip. Similar experiences have been recorded by us with the American Optical Company QRS blocking demand pacer. The implications of these latter observations to clinical situations are obvious. Patient exposure to electrical interference may result in pacer inactivation and syncope due to asystole or marked ventricular bradycardia. Under these interference circumstances, the Ektacor QRS synchronous demand pacemaker functions in a completely different fashion (Figs. 21-23). In Figure 21, an Ektacor demand pacer had been implanted on the epicardial left ventricular wall at the time of thoracotomy, for Beall prosthetic mitral valve replacement for severe mitral regurgitation. Atrial standstill and/or S-A block, sinus rhythm, atrial fibrillation, and atrial tachycardia with marked ventricular bradycardia had all been observed preoperatively. A temporary bipolar atrial pacing catheter attached to a Medtronic external pacer was passed into the right atrium to record the

right atrial electrogram. When Medtronic stimuli were applied to the right atrial catheter at a rate of 113/min, the Ektacor pacer interpreted each Medtronic stimulus as a QRS complex and produced a stimuli of its own. The ventricular and atrial rates were therefore identical, i.e., 113/min. The brachial arterial pressure curve is seen below the electrocardiogram, lead 2. The numbers 1 to 10 refer to the Medtronic pacer stimuli, "M" refers to Medtronic, and "E" refers to Ektacor. In Figure 22, the right atrial pacer is intermittently turned on at a rate of 200/min. The atrial rate is 200 at these times but the ventricular rate is 100 because of the 0.5 second refractory period in this particular Ektacor unit. When the Medtronic unit is turned off, spontaneously conducted underlying rhythm is revealed, during which the Ektacor stimuli deforms the QRS complex, but does not initiate this complex. In Figure 23, the atrial rate is intermittently increased to 400/min with 4:1 block at these times. The Ektacor QRS synchronous pacer cannot thus be turned off by external electrical interference. Demand pacing with a QRS blocking demand pacer (Electronics for Medicine wall unit) is shown in Figure 24. Electrical artefacts produced by calibration artefact and arm motion inactivate the demand pacer as the electrical artefacts are misinterpreted as QRS complexes. High amplitude P waves may also inactivate the QRS blocking demand pacer as in Figure 25, in which the second P wave superimposed on the T wave is misinterpreted as a QRS complex.

One minor problem with the electrocardiographic interpretation of the Ektacor pacer is shown in Figure 26. Three types of QRS complexes are evident. The first two complexes in strip one are conducted beats. The stimuli artefacts distort the QRS complex, which is initiated with an upward deflec-

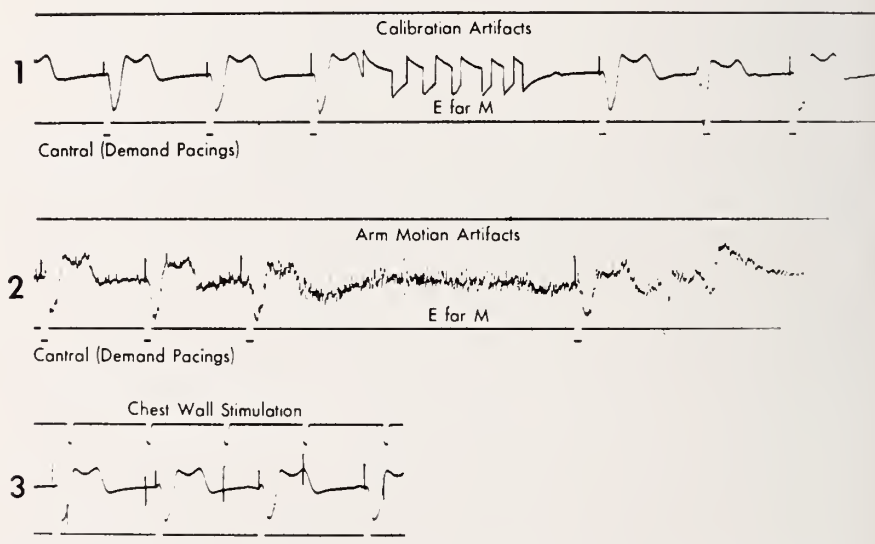


FIG. 24. Inactivation of QRS blocking demand pacer by calibration artefacts and electrical artefacts produced by arm motion (see text).

CROUCH

4:30 p. m.

5-23-68

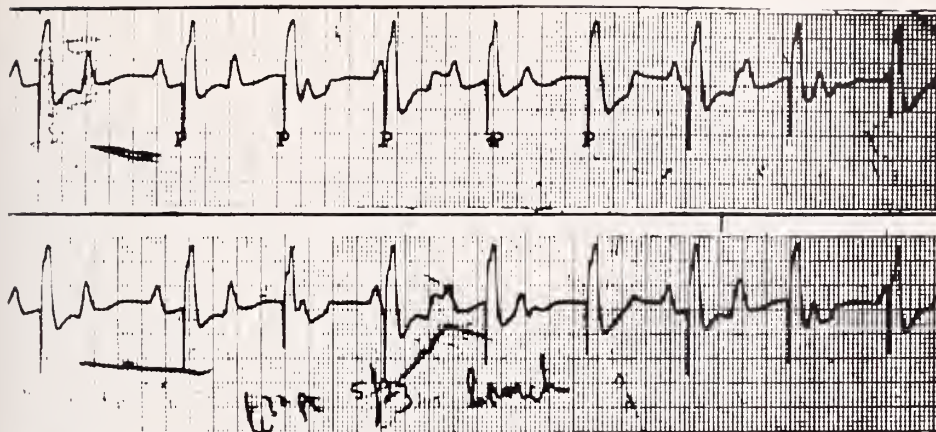


FIG. 25. Inactivation of QRS blocking demand pacer by tall P wave (see text).

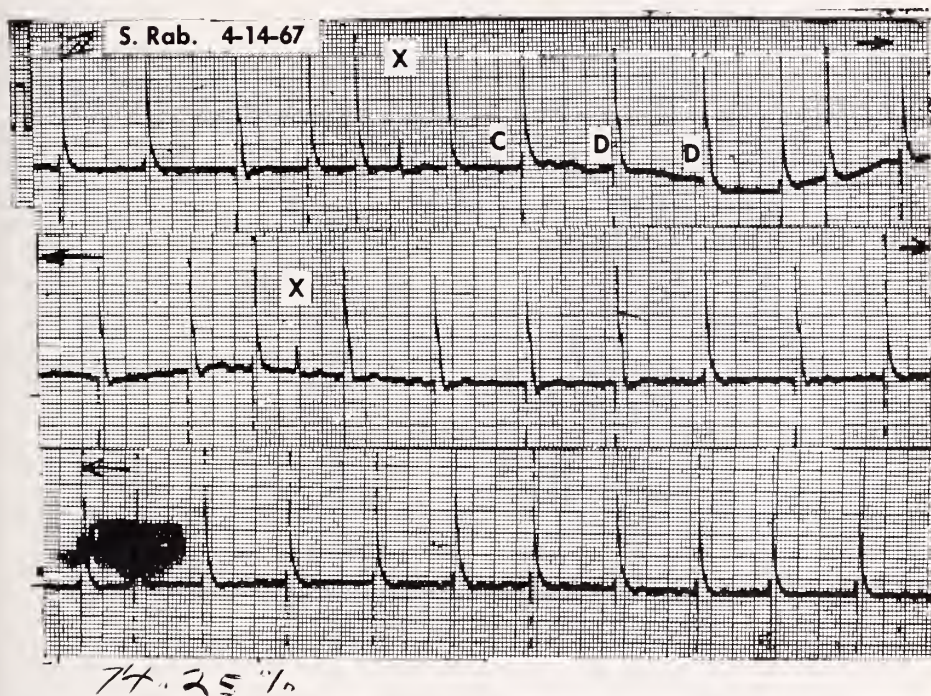


FIG. 26. Varied types of QRS complexes and pacer stimuli combinations during Ektacor QRS synchronous demand pacing in patient with atrial fibrillation (see text).

tion. The third complex in strip one is a paced beat at a rate about 70. The fourth and fifth beats are conducted beats followed by a QRS complex, without a pacer artefact. The sixth QRS complex follows the preceding pacer stimulus by an interval of about 0.4 seconds, within the refractory period of

WHITNEY, Herbert #44696

10-25-68

9:10 p. m.

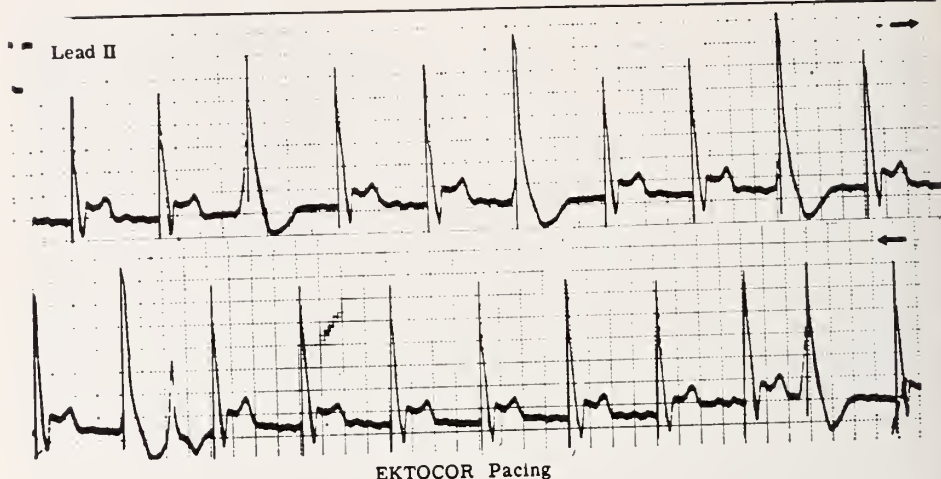


FIG. 27. Failure of Ektocor demand pacer to sense a ventricular premature beat (see text).

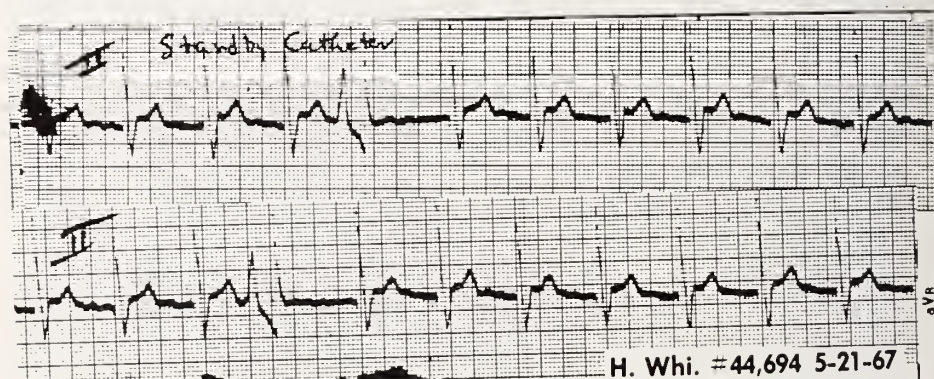


FIG. 28. Failure of a permanent QRS blocking Medtronic demand pacer to sense a ventricular premature beat (see text).

this Ektocor unit. The latter is therefore refractory and does not produce a stimulus artefact in reponse to the QRS complex marked "X".

The refractory period of the Ektocor unit results in non-sensing of the early ventricular premature beat. The following pacer stimulus could in theory occur on the T wave of the ventricular premature complex, and result in ventricular repetitive firing. The problem is illustrated in Figure 27, second strip. Reducing the refractory period from 500 to 400 m sec has partially, but only partially, alleviated the problem. It must be stressed that all demand units, QRS synchronous units, Medtronic, Ektocor, American Optical, Electronics for Medicine, and Cordis, all may fail to sense premature ventricular beats, as in Figure 28, a Medtronic pervenous demand permanent pacer.

page 3

Schwam, Frieda

4-5-68

10:20 AM

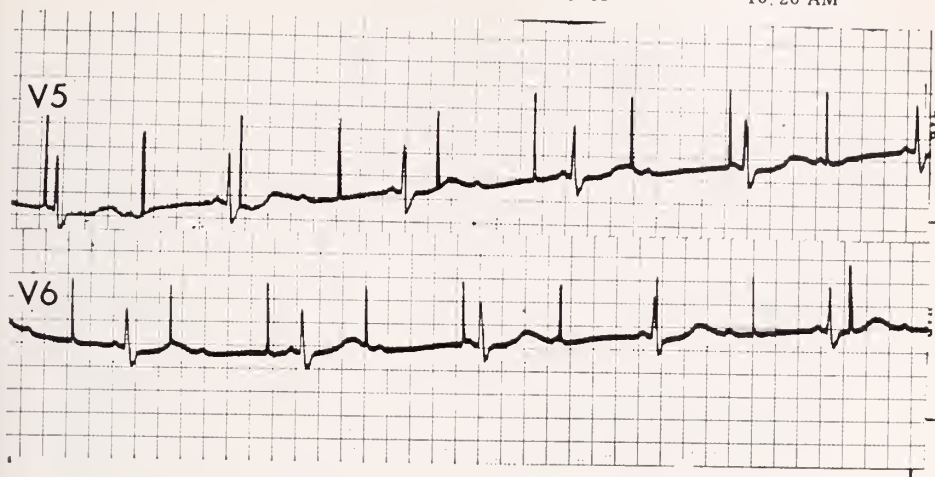


Fig. 29. Ineffective pacing (see text).

SCHWAM, Frieda

4-6-68

0750

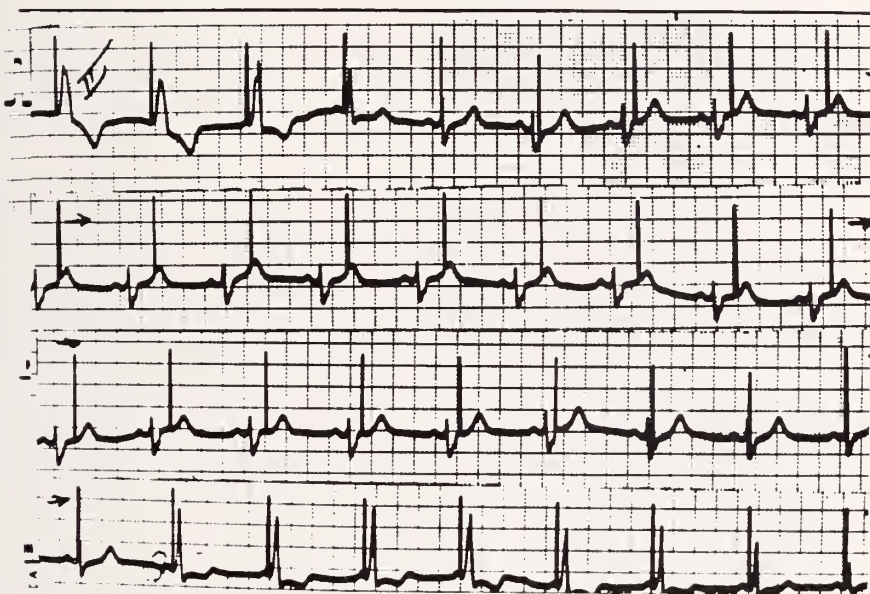


FIG. 30. Same patient as in Fig. 29. In both instances, the temporary catheter tip is passing into the pulmonary artery from the right ventricular outflow tract and fails to detect the QRS complexes at all times (see text).

Problems in Pacer Electrocardiographic Interpretation

A) A 75-year-old white woman was admitted with syncopal episodes due to intermittent 2:1 atrioventricular block. A temporary bipolar catheter was passed into the right ventricle and connected to a demand Medtronic external unit. Good capture was

COHEN, Joseph

2-20-68

1735

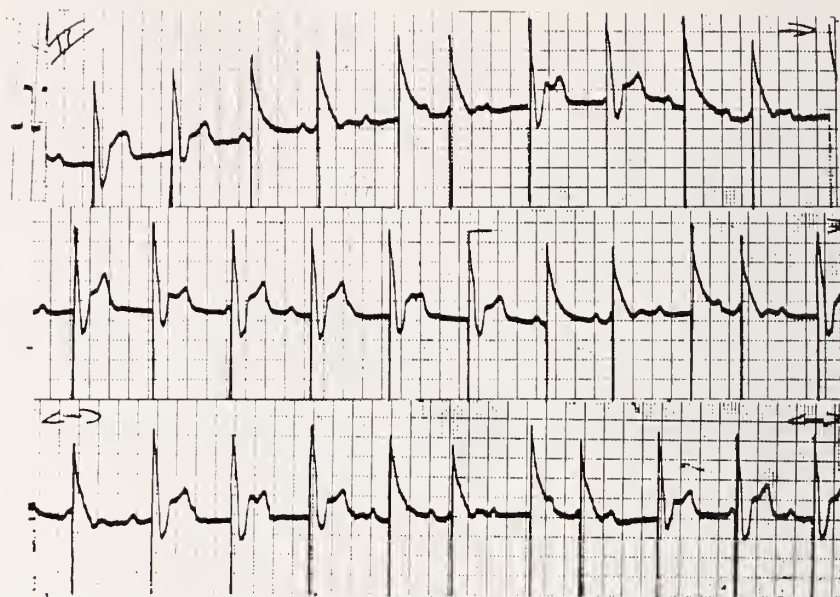


FIG. 31. Ektacor pervenous permanent pacing. Pacing is intermittent. The catheter tip has partially perforated the right ventricular myocardium (see text).

COHEN, Joseph

2-21-68

1040

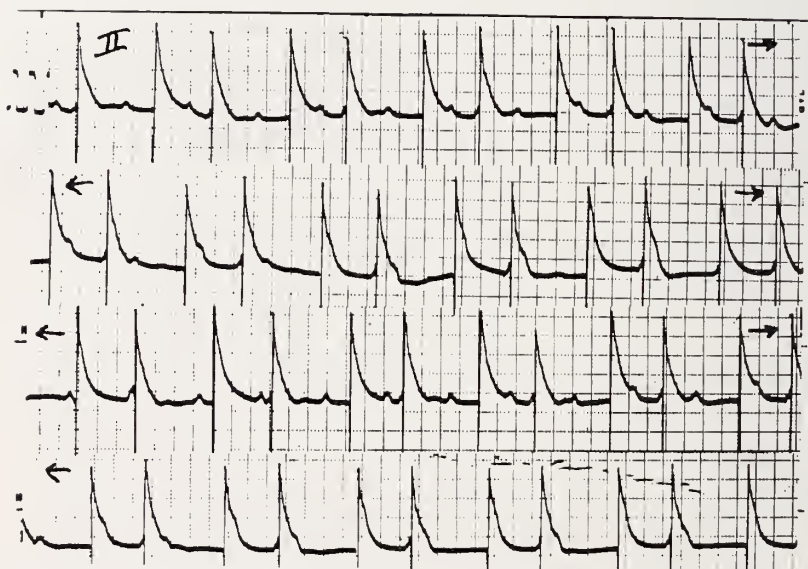


FIG. 32. Same patient as in Fig. 31. QRS complexes are sensed from the pericardium but the pacer stimuli are ineffective when the catheter tip is in the pericardium (see text).

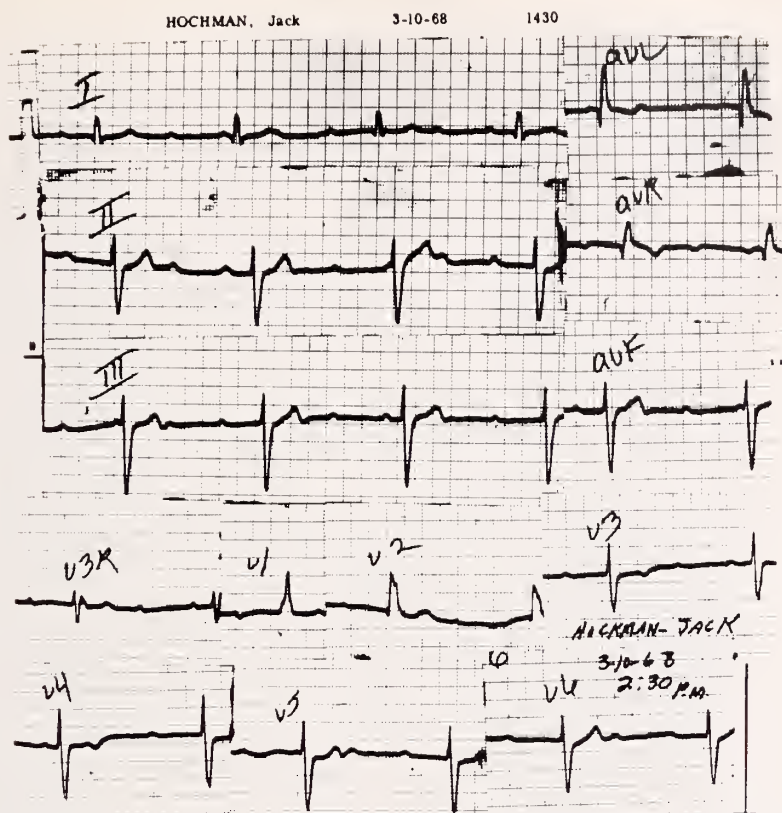


Fig. 33. Complete heart block in patient with prior sinus rhythm and right bundle branch block and left axis deviation (see text).

obtained initially, but on April 5, 1968, complete capture was lost (Figs. 29 and 30). In Figure 29, 2:1 A-V block was present with an atrial rate of 75. Fixed rate ineffective pacing is evident both in ventricular systole and diastole. On April 6, 1968, as seen in Figure 30, effective stimuli are noted in the first three complexes, strip one. Fusion complexes are present in the fourth QRS of strip one and the middle seven complexes of strip four. The other stimuli fall in the absolute refractory period and are therefore ineffective. At fluoroscopy, the catheter tip was intermittently passing from the right ventricular outflow tract to the main pulmonary artery where QRS sensing is absent; in this latter position, pacing stimuli are also ineffective. Demand ventricular pacing requires insertion of the catheter tip into the right ventricular apex to insure optimal sensing of the QRS complex. The right ventricular outflow tract is no longer utilized even for temporary pacing in our laboratory.

B) A 76-year-old male was admitted with Stokes-Adams episodes due to complete heart block and a ventricular rate of 35/min. An Ektacor demand pacer was implanted and functioned well for several days until the pulse rate became irregular (Fig. 31). The latter figure provides an interesting study. The first two complexes in the upper strip are paced beats. The third stimulus is ineffective while the fourth complex is preceded by a P wave. The latter QRS, a conducted beat, is sensed by the pacer and is distorted by a premature stimulus. The fifth stimulus is ineffective and is followed by a P wave and a conducted QRS, which is sensed by the pacer. The next two beats are pacer

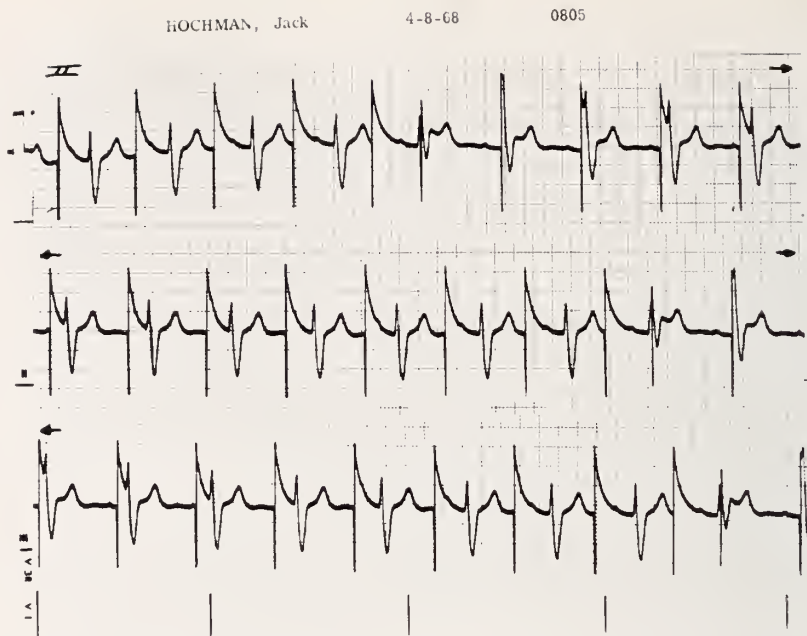


Fig. 34. Same patient as in Fig. 33. The Ektacor catheter tip has again perforated the right ventricular myocardium and is in the pericardium (see text).

initiated beats which are followed by two ineffective stimuli. In the middle strip, the first six beats are pacer initiated. The seventh stimulus is ineffective. The eighth stimulus interrupts a P conducted QRS sequence. The next stimulus is ineffective and is followed by a conducted QRS complex sensed by the pacer. The last complex is pacer initiated. A tracing the next day, as seen in Figure 32, revealed that none of the stimuli were effective. The pacer stimuli were either distorted pacer sensed QRS complexes, or were ineffective. The catheter tip had penetrated the right ventricular myocardium, partially in Figure 31, and completely in Figure 32. Withdrawal of the catheter tip into the right ventricle restored normal pacer activity.

C) The next patient is a 75-year-old white male with transient complete heart block at the onset of acute myocardial infarction. After restoration of normal sinus rhythm, the P-R interval was prolonged 0.22 seconds; complete right bundle branch block and left axis deviation were also noted. These latter three findings strongly suggested bilateral bundle branch block. Complete heart block, Figure 33, subsequently developed with multiple dizzy spells. The QRS patterns during complete heart block were identical to those during first degree atrioventricular block, suggesting that the pacer focus was in the atrioventricular junctional area with right bundle branch block and left axis deviation. An Ektacor demand pacer was implanted pervenously on April 6, 1968. Normal sinus rhythm with normal pacer activity was present on April 7, 1968. The latter evening, the patient noted a tic-like sensation in the left chest at a rate of 70/min. The next day the pulse rate became irregular (Fig. 34). The latter electrocardiogram revealed an inconstant relationship between the pacer stimuli and the QRS complexes. The pattern was puzzling until the significance of the left chest sensation was recognized. The catheter tip had perforated the right ventricular myocardium and entered the pericardium. In Figure 34, the Ektacor pacer stimuli and the QRS complexes both occur at regular intervals, except for a single early pacer stimulus in each strip. The catheter is in the pericardium, and therefore the pacer stimuli are ineffective in producing ventricular

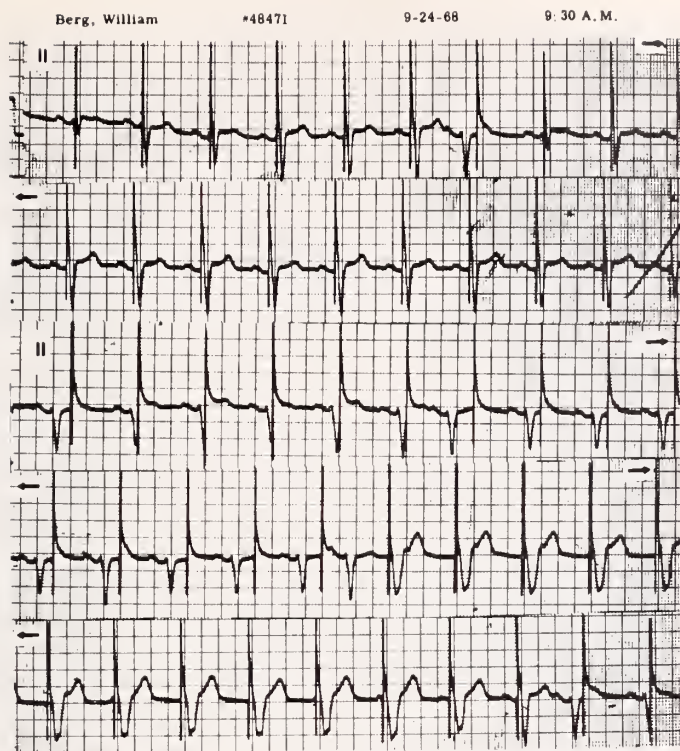


FIG. 35. Conversion of Ektacor demand pacer to fixed rate pacer by blood entering the implanted unit (see text).

stimulation, despite the fact that the stimuli fall during diastole. The QRS complexes each follow P waves, i.e., normal sinus rhythm is present, but the QRS complexes are not deformed by the Ektacor demand pacer stimuli because of the 0.5 seconds pacer refractory period. The QRS complexes are not sensed by the pacer because of the pacer refractory period, and in turn the pacer fires at regular intervals, but the stimuli are ineffective since the catheter tip is in the pericardium. On each of three occasions, one in each strip, the QRS complex is deformed by the pacer stimulus, because the QRS complex is recorded more than 0.5 seconds after the prior pacer stimulus. Therefore, the QRS complexes are at regular intervals throughout the entire tracing, but the pacer stimuli occur early three times when the pacer is not in the refractory period. The Ektacor catheter tip position was subsequently withdrawn into the right ventricular cavity. Demand QRS synchronous pacing was restored.

D) The next patient is a 74-year-old white male with an inferior wall myocardial infarction, with right bundle branch block and normal sinus rhythm; then, 2:1 atrio-ventricular block, with right bundle branch block. Frequent dizzy spells developed and an Ektacor demand pacer was implanted pervenously on August 2, 1968. In September 1968 recurrent dizziness developed. A tracing, Figure 35, at this time, revealed normal sinus rhythm with a rare atrial premature beat as well as areas of ventricular cardiac pacing. The pacing stimuli appeared to be at a constant rate and were ineffective in the refractory period of the cardiac cycle but were effective at other times. At reoperation the catheter tip was at the right ventricular apex and had *not* perforated the right ventricular myocardium. However, blood was found in the set screw socket of the Ektacor pacer, which is normally covered with silastic cement. The blood

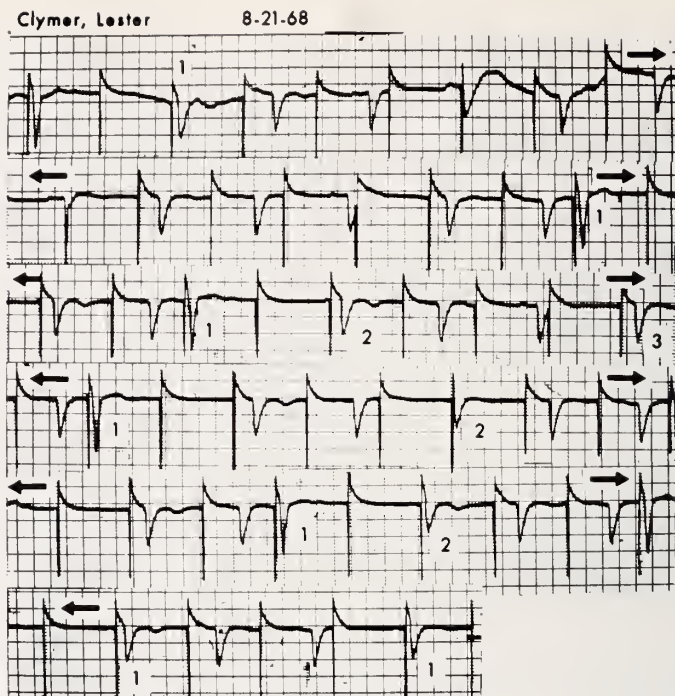


FIG. 36. Fixed rate pacing is effective only in the ventricular supernormal phase (see text).

in the set screw had inactivated the standby mechanism of the Ektacor pacer, by prevention of QRS complex sensing, which therefore functioned only as a fixed rate pacer, effective outside of the refractory period.

E) The patient is a 70-year-old white male with complete heart block and Stokes-Adams episodes. A fixed pacer was implanted elsewhere by thoracotomy. Two years later, bradycardia reappeared (Fig. 36). Fixed rate ineffective stimuli and a slow idioventricular rate predominate in Figure 36. Only periodic stimuli are effective, such as next to the last stimulus in the second strip, the third stimulus in the third strip, and the second stimulus in the fourth strip. The effective stimuli share one feature in common, i.e., they occur about 0.36–0.40 seconds after the previous spontaneous QRS idioventricular beat, i.e., in the so-called supernormal phase of the cardiac cycle. A similar phenomenon is noted in Figure 37, but in this instance the phenomenon probably involved the supernormal phase of the right atrium. Right atrial stimuli are effective only when occurring about 0.24 seconds after the preceding QRS complex. Sinus rhythm is present throughout most of Figure 36, and most of the right atrial stimuli are ineffective. The stimuli occurring 0.23–0.24 seconds after the preceding QRS complex are effective in producing atrial depolarization with consequent ventricular depolarization.

F) Interaction of a temporary fixed rate right ventricular bipolar pacing catheter, and a thoracotomy implanted P wave synchronous pacer, provides interesting electrocardiographic patterns in a 70 year-old-woman. Complete heart block, with a narrow QRS complex and Stokes-Adams episodes in 1963, led to implantation of the P wave synchronous pacer in 1963. A second Atriacor replaced the first unit in 1965 (Fig. 38). Complete heart block and a syncope episode reappeared on September 22, 1967,

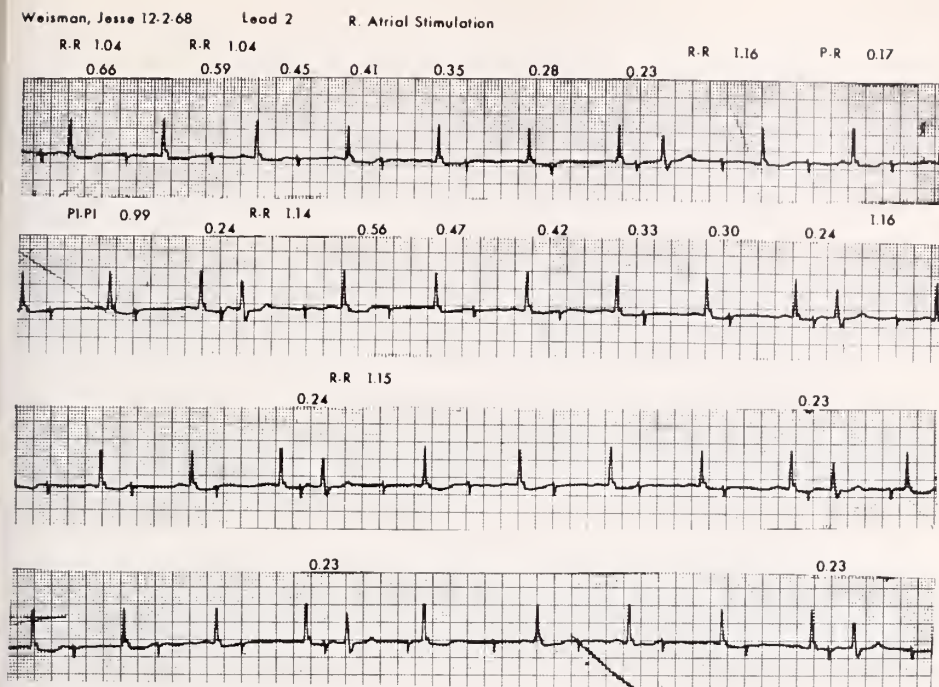


FIG. 37. Atrial pacing successful only in the atrial supernormal phase (see text).

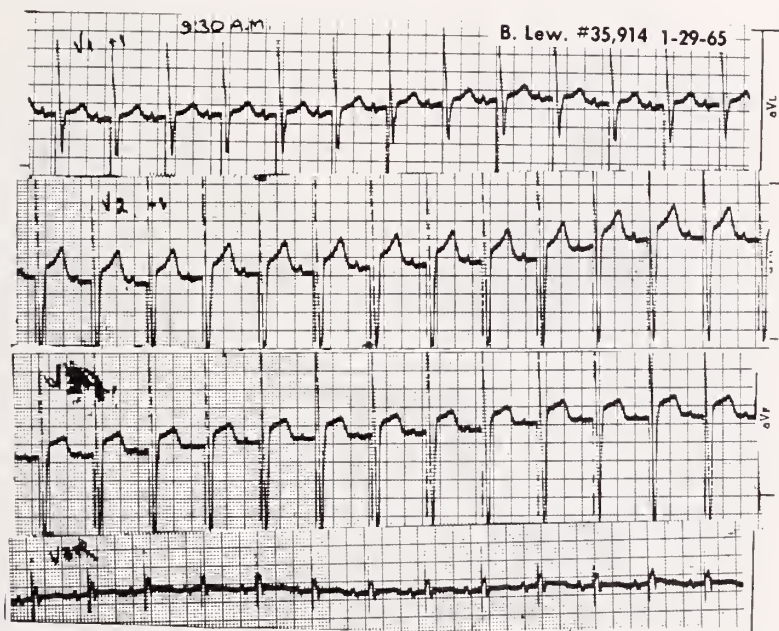


FIG. 38. P wave synchronous pacer implanted by thoracotomy in 1963 (see text).

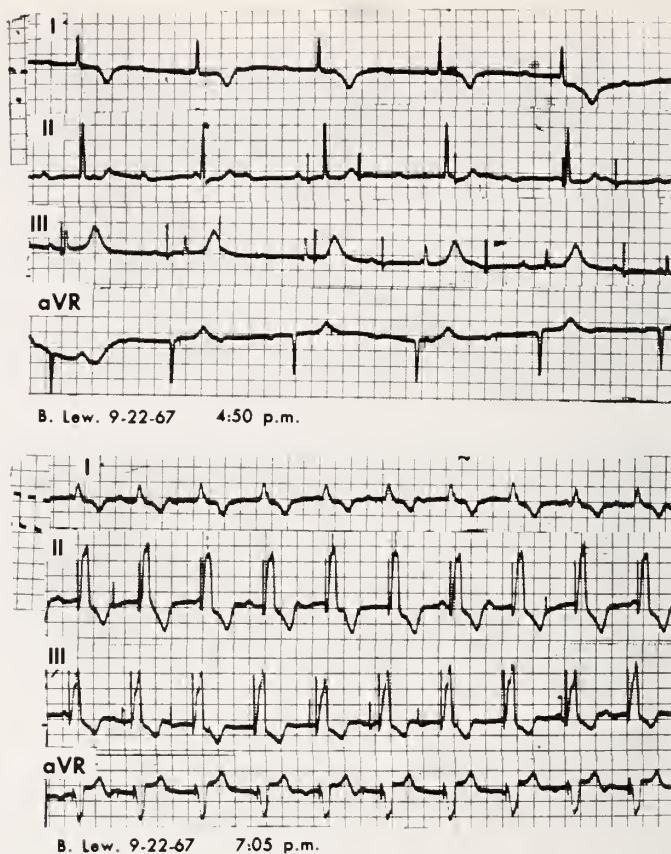


FIG. 39. *Upper strip*: Loss of P wave synchrony and loss of ventricular capture. Same patient as in Fig. 38 (see text).

Lower strip: Fixed rate temporary pervenous right ventricular pacing (see text).

4:50 PM, Figure 39, upper half. The latter illustrates several pacer abnormalities. The P wave is not detected by the atrial pickup unit. Secondly, the pacer stimuli are ineffective in producing ventricular stimuli and appear at an irregular rate, instead of a constant rate of 60/min. A right ventricular temporary bipolar catheter pacer was inserted to pace asynchronously at a rate of 75, Figure 39, 7:05 PM. In addition to the effective fixed rate Medtronic temporary catheter pacer stimuli, smaller ineffective stimuli are evident from the P wave synchronous pacer. The next day, however, the P wave synchronous pacer spontaneously became functional, as seen in Figure 40, resulting in alternating stimulation of the right ventricle by the temporary fixed rate pacer, and left ventricular stimulation by the Atricor unit. In the fifth strip, the temporary catheter pacer was transiently turned off; normal P wave synchronous pacing was then observed. In the first strip of Figure 40, the first five full P stimulus QRS complexes all demonstrate synchronous pacer stimulation. Small temporary catheter Medtronic pacer stimuli fall in the absolute refractory period and are ineffective. The next fifth Medtronic stimulus is effective, resulting in a QRS complex that is in turn interrupted by a synchronous pacer stimulus. The Atricor (Cordis) unit detected the Medtronic stimulus, interpreted it as a "P" wave (the P wave synchronous pacer would interpret any electrical stimulus of sufficient strength as a "P" wave), and fired an ineffective stimulus interrupting the sixth QRS

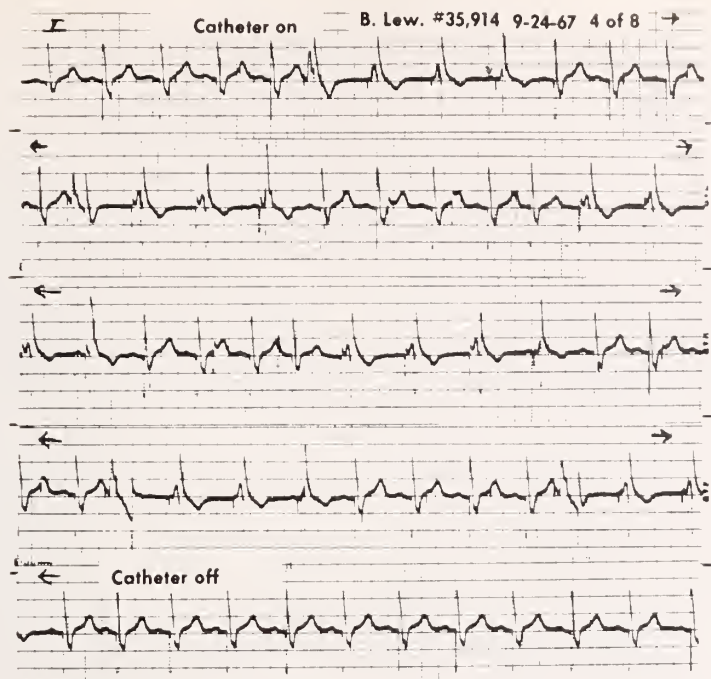


FIG. 40. Competition between P wave synchronous pacer and right ventricular fixed rate pacing. Same patient as in Fig. 39 (see text).

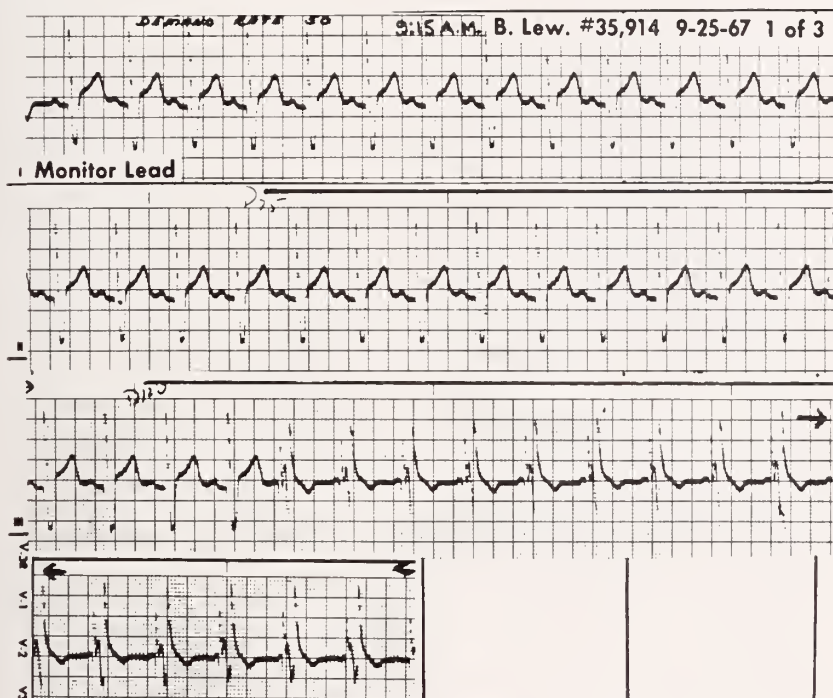


FIG. 41. Same patient as in Fig. 40. Solution of clinical problem by demand pacing at 100/min (see text).

complex. The same sequence occurs in the next three beats. The last three complexes in the first strip illustrate synchronous pacing with small ineffective, barely visible Medtronic stimuli. In the middle three strips, alternate P wave synchronous left ventricular and fixed rate right ventricular paced complexes are evident.

Clinical care at this point posed a problem because of the danger of ventricular repetitive firing during the competitive pacing. The temporary solution lay in utilizing a temporary demand Medtronic unit in place of the fixed rate unit. Since the sinus rate was 95, P wave synchronous pacing resulted when the demand rate was set below 95. When the demand rate was set at 100, the form of the QRS complex was altered with right ventricular demand pacing. The demand unit provided stimuli at a rate of 100, which are interpreted as "P" waves by the synchronous unit; the latter provides a stimuli falling in the absolute refractory period of the QRS complex stimulated by the right ventricular demand pacer (Fig. 41). The next day the defective Atracor unit was replaced and the temporary right ventricular pacing catheter withdrawn.

Summary

The various types of atrial and ventricular pacing modes are outlined, including atrial and ventricular pacing; fixed rate; P wave synchronous and blocking; and synchronous demand pacing. Examples of the varied types of resulting electrocardiographic patterns are illustrated. Interesting electrocardiographic patterns are shown. It is essential for the modern cardiologist to be familiar with these varied clinical pacing modes and the corresponding electrocardiographic patterns.

References

1. Zoll, P. M., Linenthal, A. J., Normal, L. R., Paul, M. E., and Gibson, W.: Use of External Electric Pacemaker in Cardiac Arrest, *JAMA* 159:1428, 1955.
2. Furman, S., and Schwedel, J. B.: An Intracardiac Pacemaker for Stokes-Adams Seizures, *New Eng J Med* 261:943, 1959.
3. Chardack, W. M., Gage, A. A., and Greatback, W.: Correction of Complete Heart Block by a Self-contained and Subcutaneously Implanted Pacemaker, *J Thorac Cardio Surg* 42:814, 1961.
4. Nathan, D. A., Center, S. Samet, P., Wu, C. Y., and Keller, W.: The Application of an Implantable Synchronous Pacer for the Correction of Stokes-Adams Attacks, *Ann NY Acad Sci* 111:1093, 1964.
5. Lagergren, H., et al: 305 Cases of Permanent Intravenous Pacemaker Treatment for Adams-Stokes Syndrome, *Surgery* 59:494, 1966.
6. Siddons, H.: A New Technique for Internal Cardiac Pacing, *Lancet* 2:1204, 1963.
7. Center, S., Castillo, C. A., and Keller, W.: Permanent Pervious Synchronous Pacing of the Heart, *Ann Thorac Surg* 4:218, 1967.
8. Lemberg, L., Castellanos, A., Jr., and Berkovits, B.: Pacemaking on Demand in A-V Block, *JAMA* 191:12, 1965.
9. Sowton, E., Leatham, A., and Carson, P.: The Suppression of Arrhythmias by Artificial Pacemaking, *Lancet* 2:1098, 1964.
10. Heiman, D. F., and Helwig, J., Jr.: Suppression of Ventricular Arrhythmias by Transvenous Intracardiac Pacing, *JAMA* 195:1150, 1966.
11. Lister, J. W., Cohen, L. S., Bernstein, W. H., and Samet, P.: Treatment of Supraventricular Tachycardias by Rapid Atrial Stimulation, *Circulation* 38:1044, 1968.

Received for publication January 22, 1969

Cancer of the Nasopharynx:

A Study of Ninety Cases

SAMUEL M. BLOOM, M.D., F.A.C.S.

Introduction

Cancer of the nasopharynx is a serious disease with a formidable mortality, and difficult early diagnosis. The onset is insidious, the primary site is hidden, and the manifestations are protean. This paper presents an analysis of the clinical picture, course, and histopathological findings of a series of 90 cases followed from 1 to 33 years, with the major emphasis on factors affecting the prognosis.

Fifty-five patients were selected from the ward service, 20 were referred to the hospital by staff physicians, and 15 came from the author's private practice.

Pathological Findings

The cellular type of the tumor is the most significant prognostic factor in cancer of the nasopharynx (1, 2). In 1921 Schmincke (3) in Germany described the tumor now bearing his name as "a cellular, diffusely infiltrating growth whose uniqueness rests in the syncytial structure which is permeated by lymphocytes. The cells are large, with rounded or oval vesicular nuclei showing nuclear atypism, numerous mitoses, and varying amounts of chromatin with one or two prominent nucleoli. They occur in anastomosing cords or trabeculi and in nests, or islands. Occasionally they break away and in areas may resemble sarcoma." Schmincke stated further that the epithelial nature of the tumor was evident from the cellular and nuclear structure, type of growth, and relation to the lymphoid stroma. He believed that the tumor arose from the branchial clefts, and that the admixture of lymphocytes was due to the close relationship between the epithelial and the lymphatic elements, but that the lymphocytes did not participate in the neoplasm. He emphasized that these are embryonal cell carcinomas. Also in 1921, a similar tumor was reported by Regaud and Reverchon in France (4).

Through the years little has been added to improve upon Schmincke's original description. On the contrary, there have been other terms proposed which serve only to confuse the issue. Lymphoepithelioma, although widely used, is really a misnomer. It is not a tumor of lymphoid tissue. The term "transitional cell carcinoma" is also inappropriate (1). Examination of the nasopharynx reveals only two main types of epithelium (2, 5, 6, 7a). In the

From the Department of Otolaryngology, The Mount Sinai Hospital, New York, N.Y.

Associate Clinical Professor of Otolaryngology, the Mount Sinai School of Medicine of the City University of New York, N.Y.

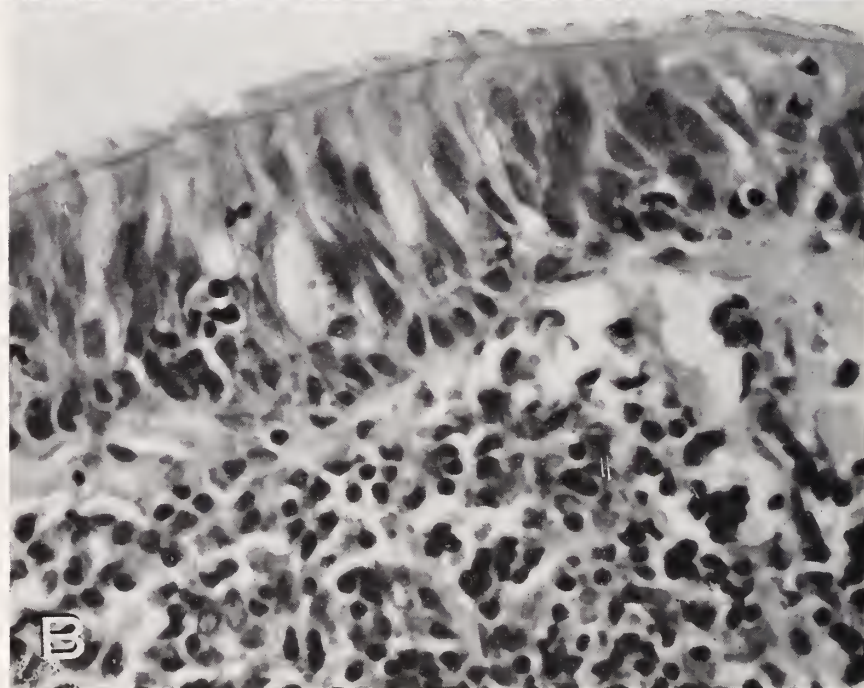


FIG. 1a. Normal ciliated pseudostratified columnar epithelium, upper portion of nasopharynx, $\times 100$.

FIG. 1b. The same, $\times 400$.

upper portion there is a ciliated pseudo-stratified columnar epithelium (Figs. 1a, b), which in the lower portion, undergoes squamous metaplasia (Figs. 2a, b). There is general agreement that most of the tumors arising in the nasopharynx are of epithelial origin (3, 4, 7b, c, d), although some authors classify the Schmincke tumor with the reticulum cell sarcomas (1, 2).

In this series 50 cases were classified as embryonal cell carcinomas (Figs. 3a, b). Other carcinomas which demonstrated characteristics of squamous cell epithelium, including intercellular bridges, have been classified as squamous cell carcinomas, immature and mature. The immature squamous cell cancer showed some differentiation of the tumor cells and epithelial architecture. There were 25 cases (Figs. 4a, b). The mature squamous cell cancer revealed well-differentiated tumor cells with keratinization and pearl formation. There were 7 of these (Figs. 5a, b). Two of the tumors were unclassified carcinomas. Sarcomas were found in only 6 cases. There were 4 cases of lymphosarcoma and reticulum cell sarcoma (Figs. 6a, b). There was one angiosarcoma, and one angiofibrosarcoma. Plasmocytoma, rhabdomyosarcoma, and chondrosarcoma have been reported but were not found in this series. The incidence of pathologic diagnoses in 90 cases is shown in Chart 1.

Stage of Disease

Stage of disease (8) is the second important factor in evaluating prognosis. Stage I is applied to those cases in which the tumor is confined to the nasopharynx. Stage II is applied to those in which there are metastases to the regional lymph nodes. Stage III is applied to those in which there is invasion of the soft palate, nasal cavity, orbit, paranasal sinuses, or base of the skull. Incidence of the cellular types by stage of disease is shown in Chart 2. There were 15 cases in Stage I, 35 in Stage II, and 40 in Stage III.

In the series studied, the five-year survival rate of patients first seen in Stage I was 53% (8 of 15); in Stage II, 34% (12 of 35); and in Stage III, 5% (2 of 40), as shown in Chart 3.

Conversely, the mortality of patients first seen in Stage I was 27% (4 of 15); Stage II, 37% (13 of 35); and Stage III, 95% (38 of 40). It is a sad commentary that the proportion of cases being referred to the hospital in Stage III is only slightly less now than it was 20 years ago. At present, the main hope for improving results of treatment lies in earlier diagnosis.

Etiology

In some cancers, contributing causative factors have been implicated. However, in cancer of the nasopharynx no etiological factor has thus far been clearly adduced (7e, 9). There is a high incidence of the tumor in the population of Southern China, especially in Kwantung Province (7f). The incidence of cancer of the nasopharynx in Hong Kong is reported as 18% of all malignant tumors (6); in a world-wide survey of white populations the average incidence is 0.25% (7g). Chinese born in other countries

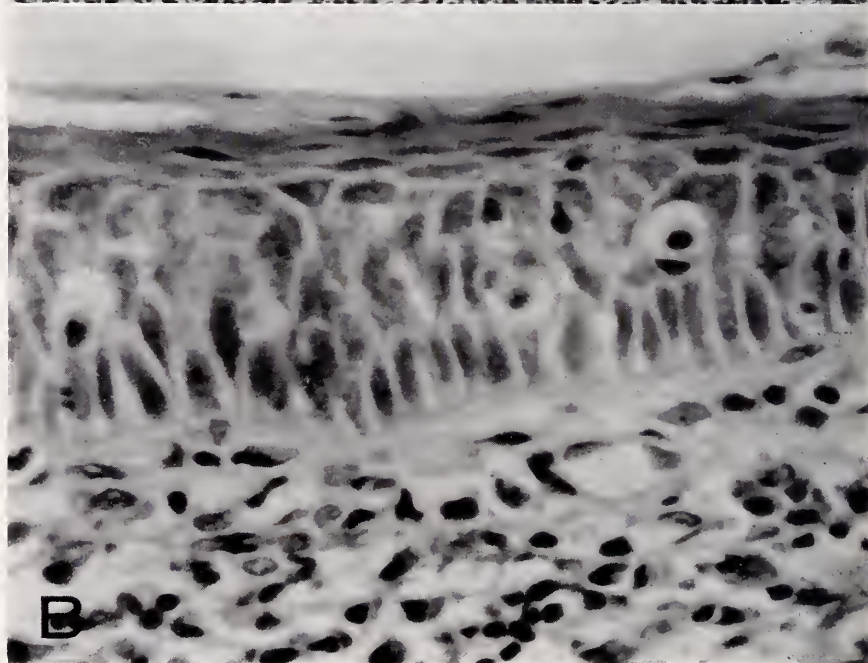


FIG. 2a. Normal squamous metaplasia of epithelium of lower portion, $\times 100$.
FIG. 2b. The same, $\times 400$.

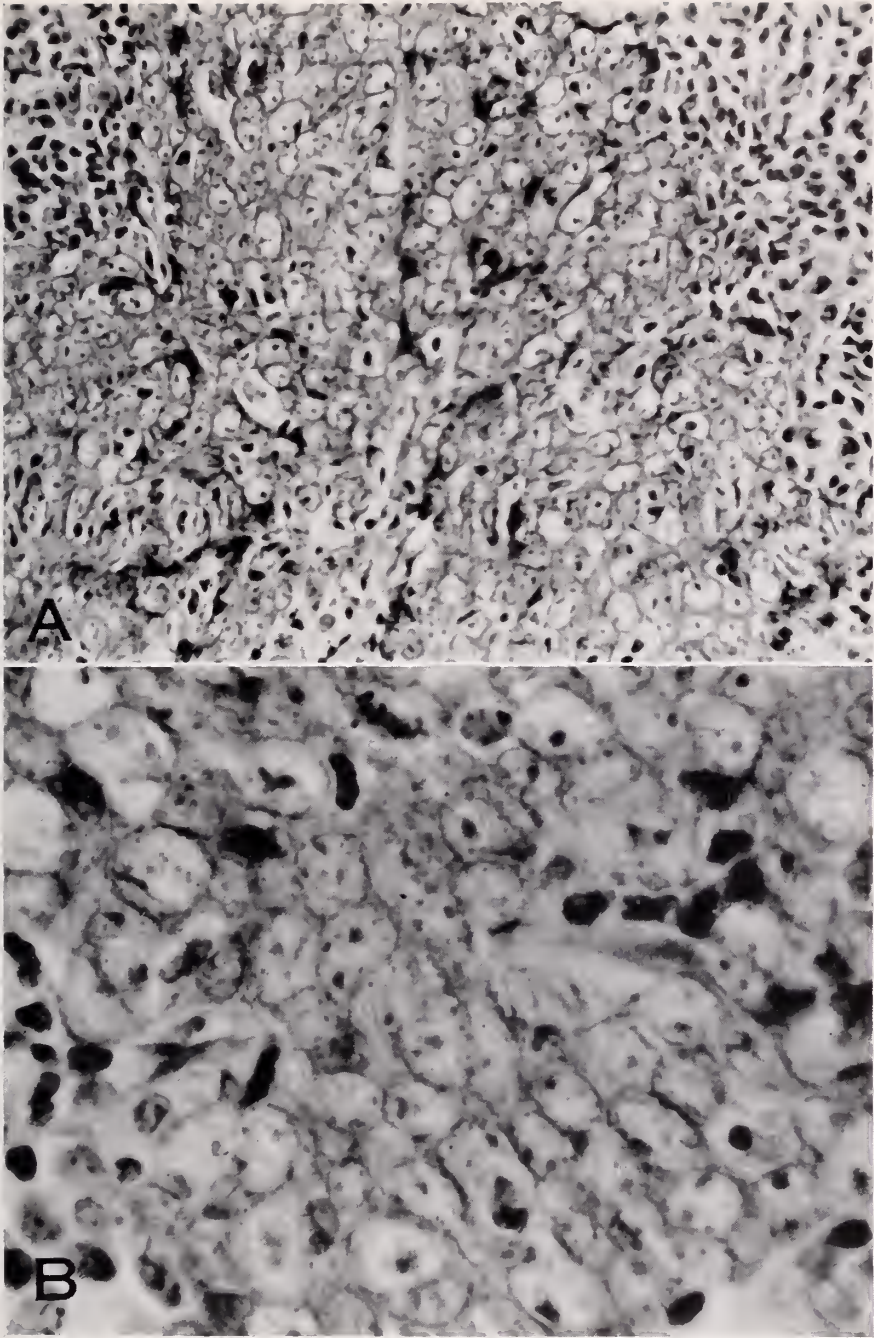


FIG. 3a. Typical embryonal cell carcinoma (Schmincke tumor), $\times 200$ (Case 57).

FIG. 3b. Higher power showing syncytial cells, with vesicular nuclei, prominent nucleoli, and frequent mitoses, $\times 400$.

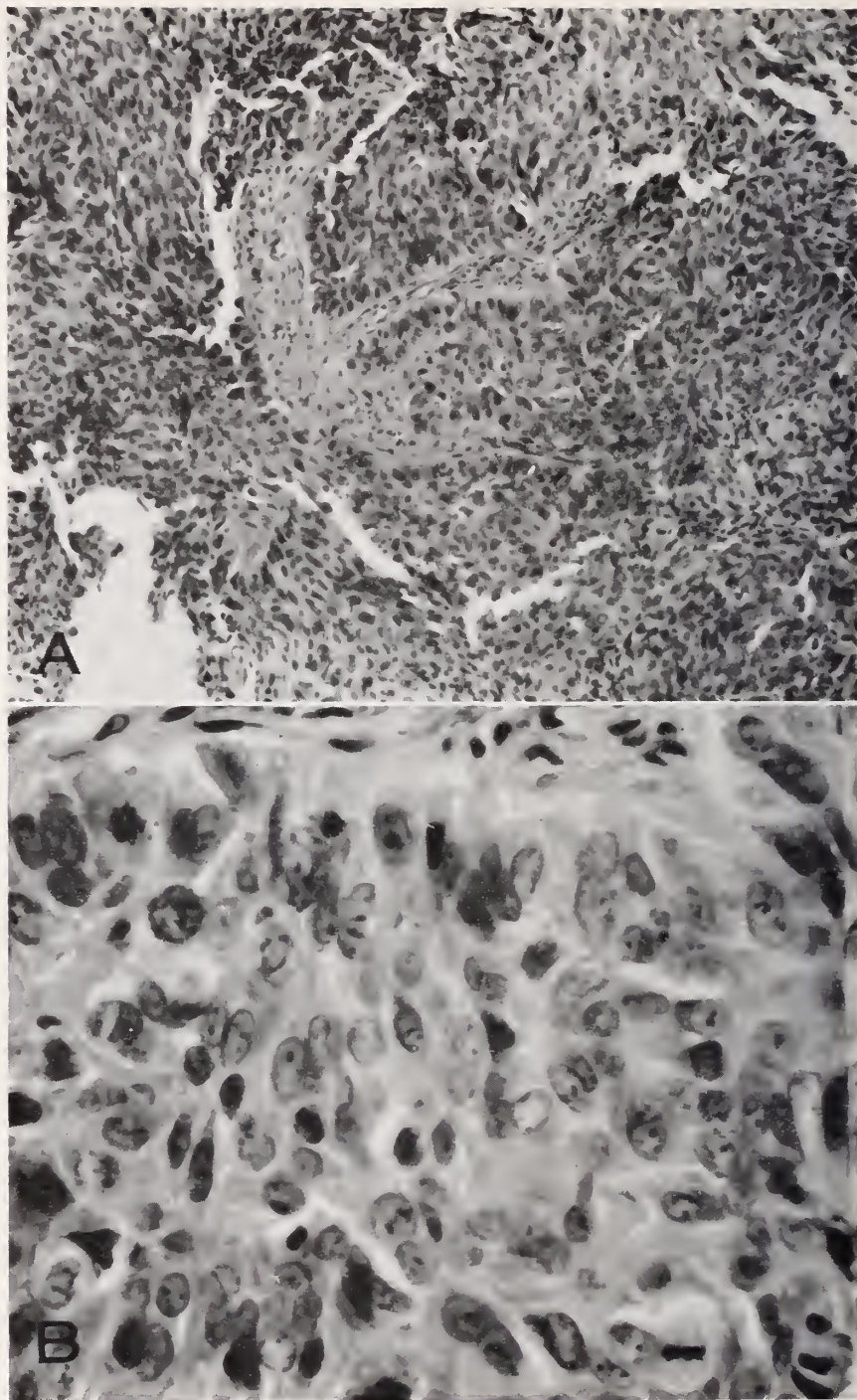


FIG. 4a. Immature squamous cell carcinoma, showing intercellular bridges, some differentiation, and numerous mitoses. $\times 100$ (Case 61).

FIG. 4b. The same, $\times 400$.

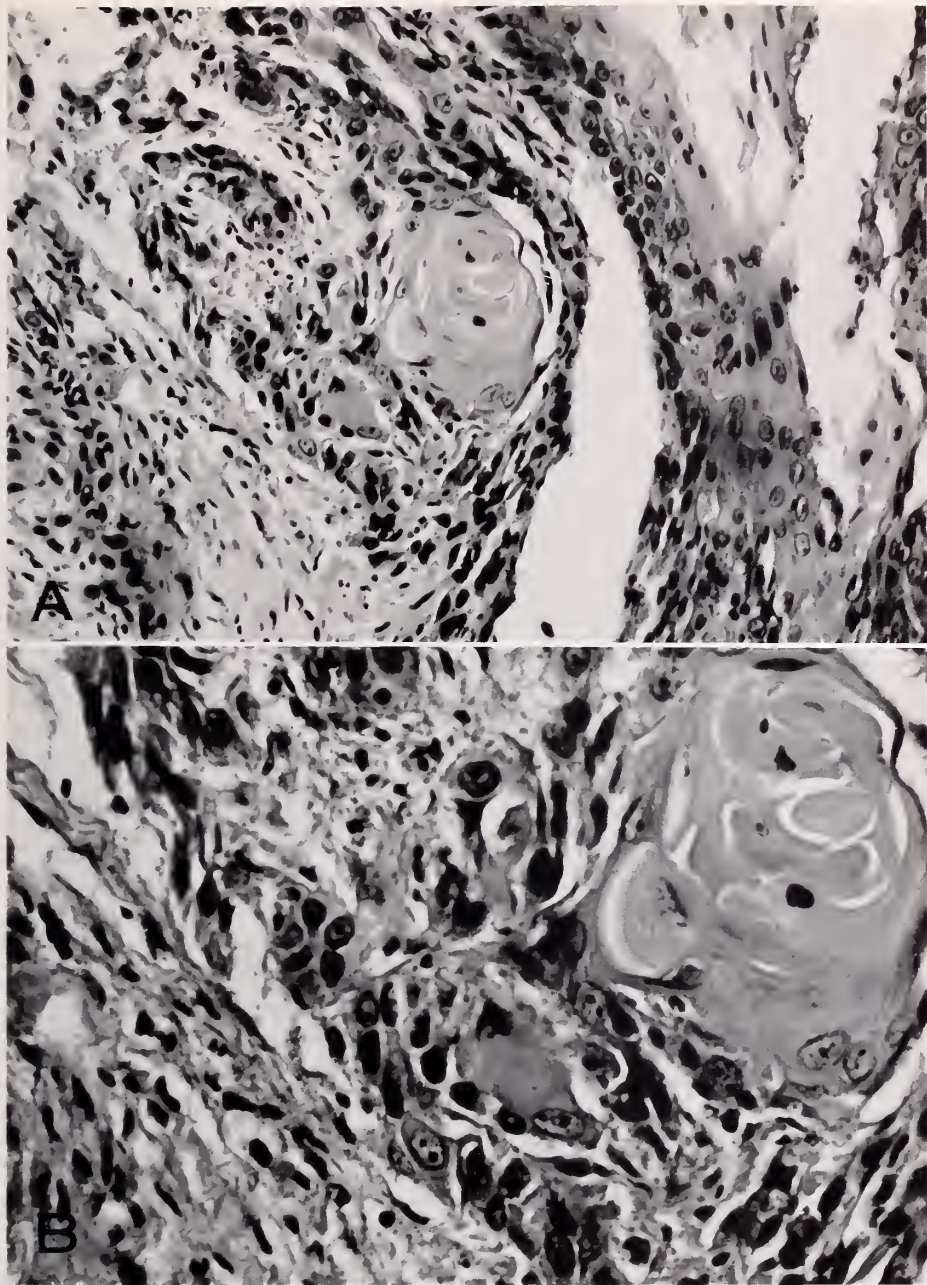


FIG. 5a. Mature squamous cell carcinoma, with keratinization and pearl formation, $\times 200$ (Case 38).

FIG. 5b. The same, $\times 400$.

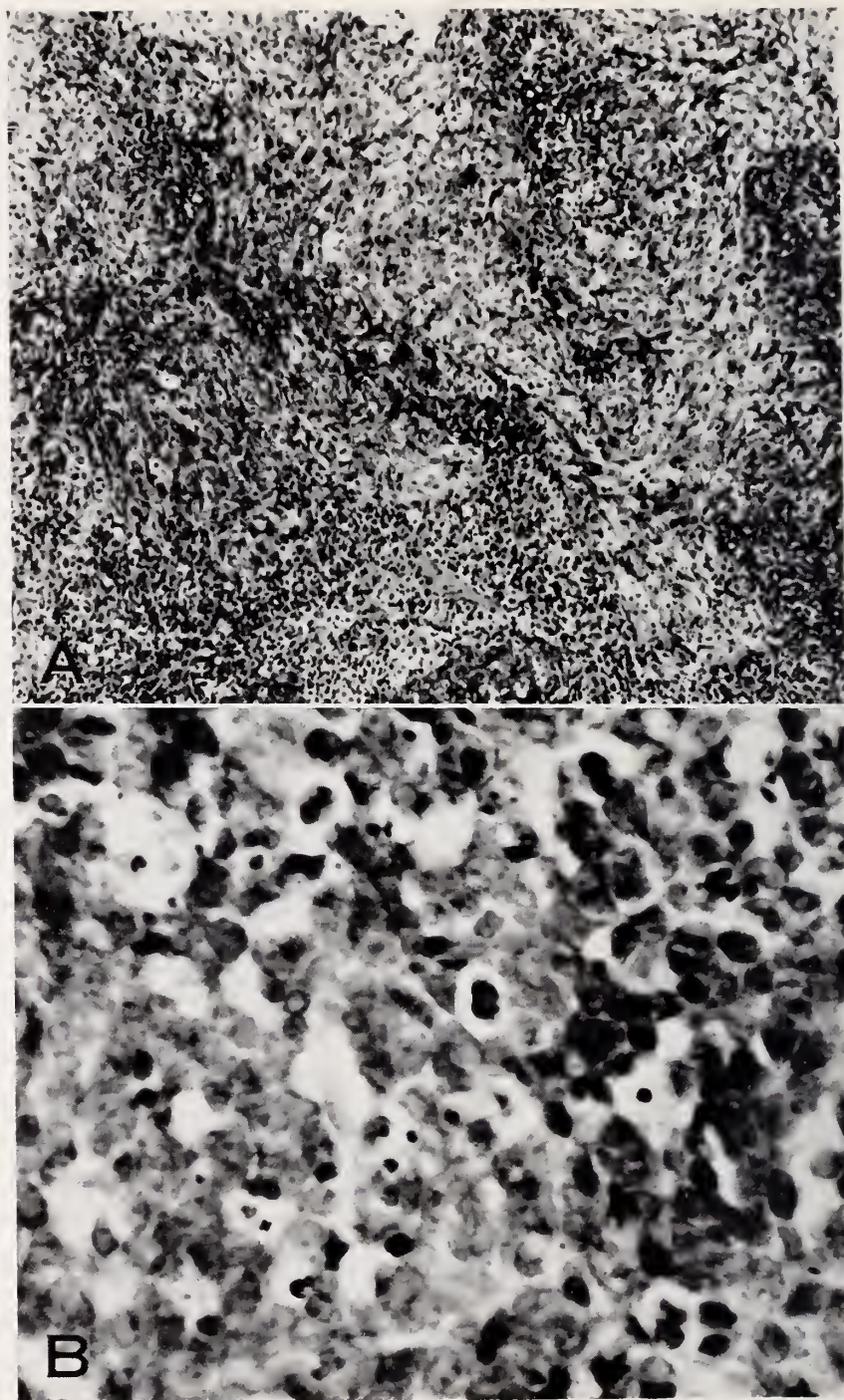


FIG. 6a. Reticulum cell sarcoma composed of tumor cells in anastomosing cords, infiltrated by mature lymphocytes, and resembling Schmincke Tumor, $\times 100$ (Case 49).

FIG. 6b. The same, $\times 400$.

INCIDENCE OF PATHOLOGIC DIAGNOSES

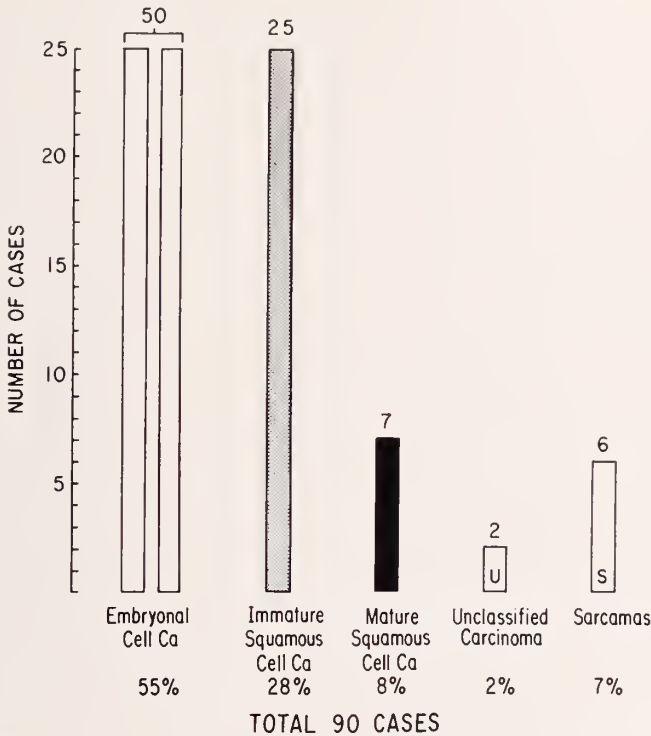
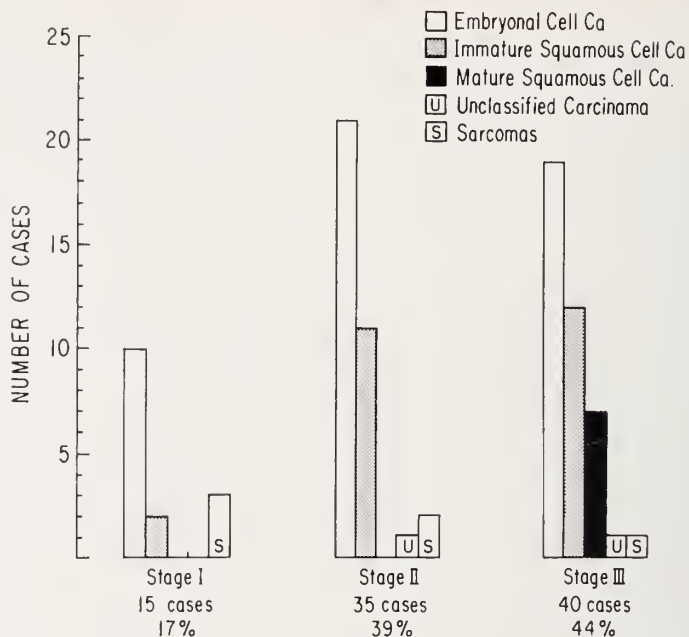


Chart 1.

also show a high susceptibility to this disease (7h, 10, 11, 12). This suggests that there is a racially linked genetic factor (2, 7e, 7h, 12, 13). In the present series 62 patients (69%) were Caucasian; 21 (23%) were Chinese; and 7 (8%) were Negro. The 23% incidence of Chinese patients in the present series contrasts with an admission rate of Chinese of less than 1% to The Mount Sinai Hospital. There were 69 males and 21 females. The ratio of males to females was 3.3 to 1.

The age at onset of symptoms ranged from 13 to 74 years. The peak incidence was in the fourth decade. Sixty percent of the cases occurred in the fourth and fifth decades. An analysis of the age incidence with reference to the microscopic findings, reveals an interesting difference in the peak incidence for the various types. The largest number of embryonal cell carcinomas occurred in the 40's. The peak incidence of the immature squamous cell carcinomas was in the 50's, and the mature squamous cell carcinomas showed the greatest incidence in the 60's. The average age at onset of disease of the patients with embryonal cell cancer was 49 years; immature squamous cell cancer, 52 years; and mature squamous cell cancer, 63 years (see Chart 4).

INCIDENCE BY STAGE OF DISEASE



Total 90 cases

Chart 2.

SURVIVAL BY STAGE OF DISEASE

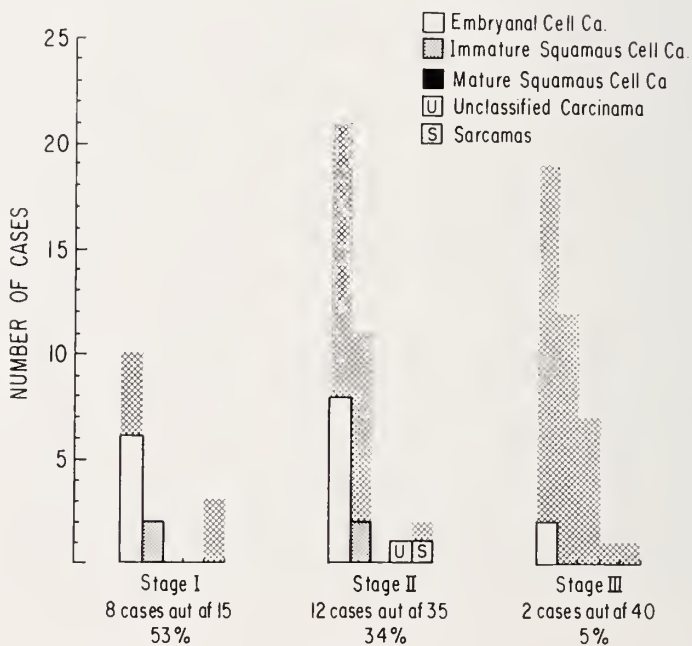


Chart 3.

Symptomatology

The symptoms of this disease are kaleidoscopic. They can be best considered under cervical, nasal, otic, ophthalmic, and neural headings. General symptoms are infrequent.

1. *Cervical Symptoms.* Enlargement of lymph nodes of the neck may be the first event which prompts a visit to the doctor. Frequently the node just beneath the posterior border of the sternomastoid muscle at the level of the angle of the jaw is the first to be noticed by the patient.

2. *Nasal Symptoms.* Early in the disease there may be none in this category. There may be intermittent stuffiness, usually unilateral, or a slight mucoid or blood-stained discharge. Late in the disease, the discharge may become fetid as a result of tumor necrosis. Anosmia was rarely noted. Involvement of the paranasal sinuses occurs late, but may be the condition which causes the patient to seek medical advice for the first time. Epistaxis also occurs late but may be severe enough to require hospitalization. In general, the occurrence of unilateral persistent nasal obstruction in a middle-aged patient should arouse suspicion of a nasopharyngeal neoplasm.

3. *Otic Symptoms.* Symptoms of Eustachian tube occlusion may be the first to bring the patient for examination. Usually unilateral, these range from a slight feeling of fullness, clicking sensations, or stuffiness, to pain and discharge. As a result of the tubal occlusion, conductive type of hearing impairment ensues. Sensorineural hearing loss and vertigo are rare. Tinnitus may be the first symptom, but is not common.

AGE AT ONSET OF DISEASE

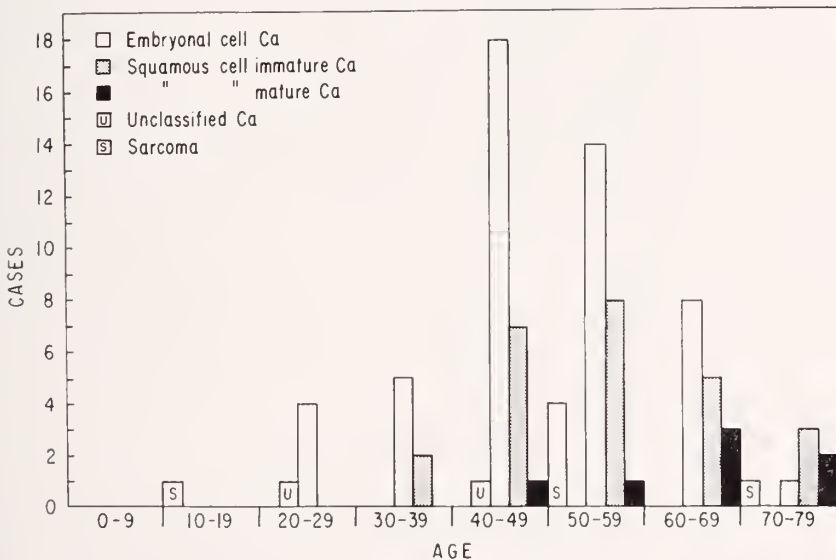


Chart 4.

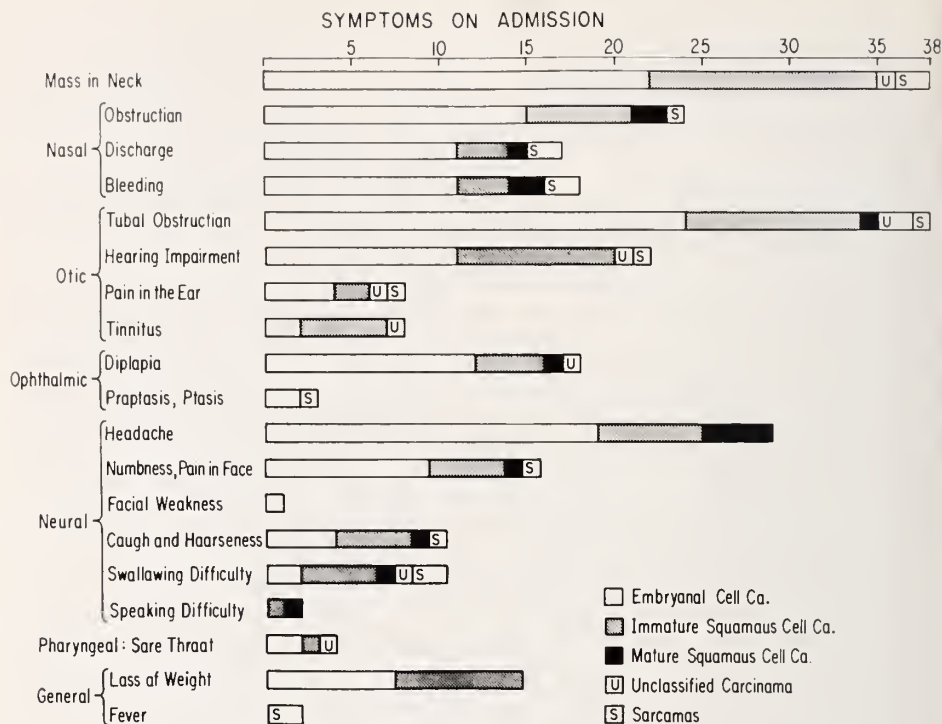


Chart 5.

4. *Ophthalmic Symptoms.* The early symptoms referable to the eyes are due to involvement of the abducens, oculomotor and trochlear nerves. The most common is diplopia. Next, in order, are ptosis, and proptosis. Loss of vision was seen only in far-advanced disease.

5. *Neural Symptoms.* The widest range of symptoms was found in this category. The most common was headache, often appearing initially as the only symptom. Next in frequency were disturbances of the trigeminal nerve, ranging from mild paresthesias and hypesthesias, to severe paroxysms of pain. Facial paralysis was the chief complaint in one patient. Difficulty in swallowing, regurgitation of food into the nose, and nasal quality of speech, were frequent. Cough and hoarseness were common. Difficulty in speech was noted. Pain and stiffness in the neck were also complaints.

6. *General Symptoms.* Loss of weight and weakness were found only in advanced cases (see Chart 5).

Physical Findings

1. *The Primary Lesion.* On casual inspection of the pharynx there may be no indication of the danger that lurks behind the palatine curtain. Bulging of the soft palate was seen in only five cases. On indirect mirror examination

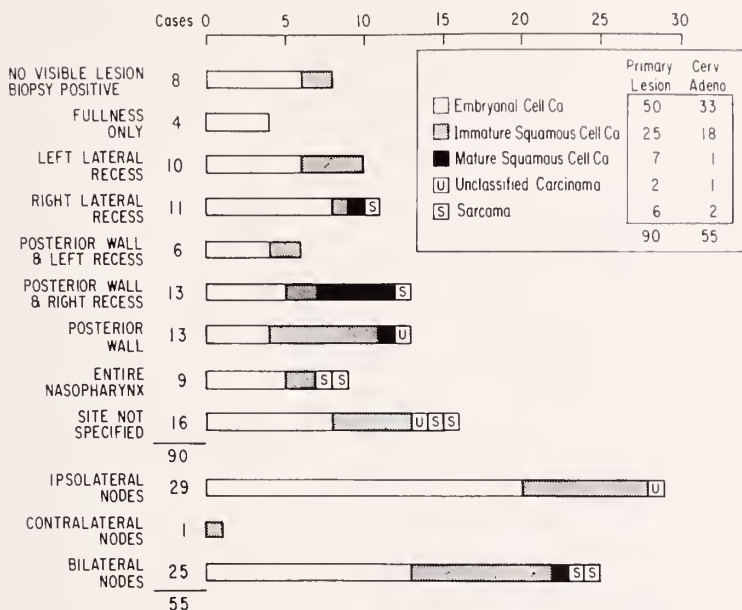
SITE OF PRIMARY LESION AND
CERVICAL ADENOPATHY ON ADMISSION

Chart 6.

of the nasopharynx there may be no visible lesion, only a fullness of the posterior wall, narrowing of the lateral recess with intact mucosa, or, there may be a slightly raised granular lesion with intact or ulcerated mucosa on the posterior wall, the vault, the lateral wall, or the lateral recess. The torus tubarius may be compressed or covered with dusky lymphoid tissue. Occasionally the lesion is exophytic in type. In the present series, biopsies were positive in eight cases in which there was no visible lesion.

2. *Cervical Adenopathy.* Enlarged cervical nodes were palpable on admission in 55 patients. The adenopathy was ipsilateral in 29, contralateral in 1, and bilateral in 25 patients (see Chart 6).

3. *Nasal Findings.* In general, the appearance of the nasal mucosa and turbinates gave no indication of disease. In only three cases neoplastic tissue was seen posteriorly, near the floor and lateral wall of the nasal cavity. The sinuses were involved by tumor only rarely.

4. *Otic Findings.* Many patients had symptoms of tubal occlusion on admission; most had a conductive hearing loss. There was a neural element in very few. Caloric responses were absent in one case. There was unilateral otitis media in two cases.

5. *Ophthalmic Findings.* The abducens nerve was most frequently involved, the oculomotor next, and the trochlear, rarely. There was unilateral proptosis in two cases, optic atrophy and papilledema in one patient.

CRANIAL NERVE INVOLVEMENT ON ADMISSION

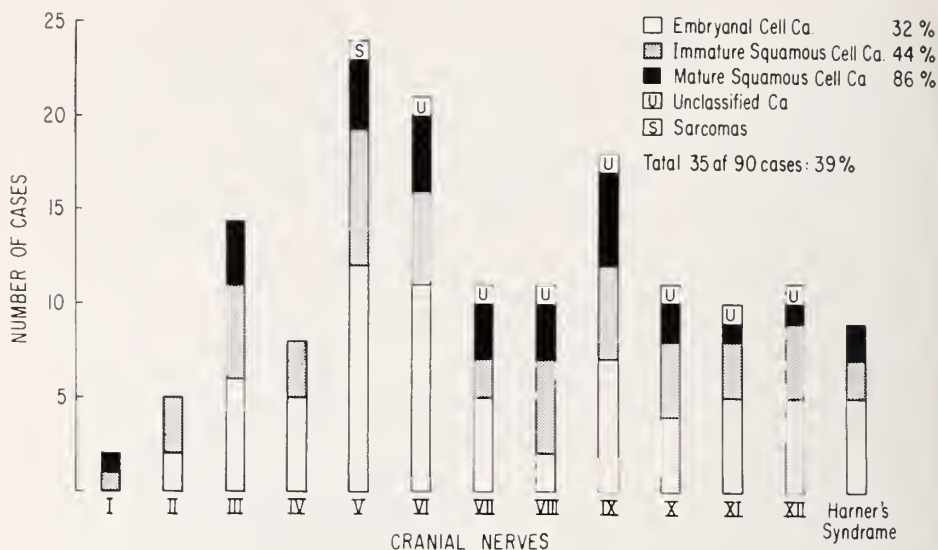


Chart 7.

6. *Neural Findings.* There was a great variety of findings in this category. The trigeminal nerve was most frequently involved (24 patients). The abducens was second (21 patients). The glossopharyngeal was next (18 patients). The vagus was involved in 11 cases; the spinal accessory, 10; the facial in 11; the auditory branch of the acoustic nerve was involved in 11; and the vestibular was rarely involved. The hypoglossal was involved in 12 cases, usually in association with the glossopharyngeal and vagus in the jugular foramen syndrome, but isolated involvement of the hypoglossal was seen once. This was due to pressure from retropharyngeal nodes, and resolved after radiotherapy. Horner's syndrome, due to involvement of the cervicosympathetic trunk, was also noted in nine cases. One patient had involvement of all 12 cranial nerves. In the present series, neurological involvement was found on admission in 35 patients (39%). In the embryonal cell carcinomas the incidence was 16 of 50 patients (32%); in the immature squamous cell carcinomas, 11 of 25 (44%); and in the mature squamous cell carcinomas, 6 of 7 (86%) (see Chart 7).

7. *Distant Metastases.* Involvement of other than regional lymph nodes, and metastasis to the liver and bones, particularly the vertebrae, also occurred.

Distant metastases were found in 20 percent of the embryonal cell and immature squamous cell carcinomas, but in none of the mature squamous cell carcinomas.

8. *Radiographic Findings.* At the base of the skull, radiographic findings ranged from slight enlargement of the foramen ovale, to destruction of the

RADIOGRAPHIC FINDINGS ON ADMISSION

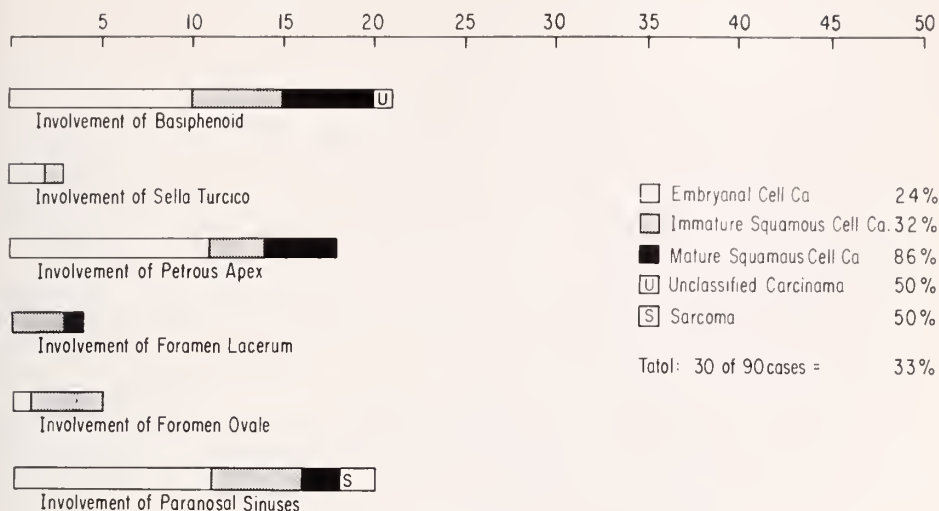


Chart 8.

body or wings of the sphenoid, the clivus, the posterior clinoids, or sella turcica. The apex of the petrous pyramid was occasionally involved. The lateral view frequently revealed a change in the contour of the air column in the nasopharynx.

Destruction of the base of the skull on radiography occurred with greater frequency in the mature squamous cell carcinomas (86%), than in the embryonal cell carcinomas (24%). A similar finding was also reported by Baclesse (14) (see Chart 8).

Diagnosis

An important factor contributing to difficulty in diagnosis is the hidden location of the nasopharynx. To add to the problem, the lesion may be submucosal. In many instances no gross alteration can be seen, yet biopsy will demonstrate the disease. Examination of the nasopharynx requires special skill. It is to be regretted that facility in using the postnasal mirror is not acquired by many examiners. Local anesthesia is helpful, and often necessary. Catheters may be drawn through the nasal cavity into the pharynx on each side and used as protractors of the soft palate to permit thorough inspection of the postnasal space (15). The electric nasopharyngoscope affords only a limited view, but may be useful in some instances.

In the presence of cervical adenopathy or cranial nerve involvement and otic, ophthalmic, nasal, or pharyngeal symptoms, the nasopharynx should be suspected as the possible source of the neoplasm. Given an adult with a lesion in the nasopharynx, cancer must be presumed present until proved otherwise (16).

Where a constellation of symptoms presents itself, biopsy is warranted even

when nothing abnormal is apparent to the naked eye; indeed, a second or third biopsy is sometimes required to prove the diagnosis. Biopsy under local anesthesia is usually an office procedure, but general anesthesia may be required.

The general practitioner should be taught to suspect disease of the nasopharynx. Most medical students are given only a smattering of instruction in otolaryngology; the nasopharynx is often entirely neglected. The author believes that if the diagnosis was suspected more often, and random biopsies were taken, the number of cases discovered earlier would be greater than at present.

Radiographs can be used for confirmation of a clinical diagnosis (1, 2, 7i, 14), but chief reliance must be placed on a thorough clinical examination and biopsy.

Primary malignant tumors in the nasopharynx are to be distinguished from the following: 1) juvenile angiofibroma; and 2) secondary growths involving the nasopharynx, including chordomas, craniopharyngiomas, glomus jugulare tumors, meningiomas, and teratomas (5).

Errors in Diagnosis and Treatment

The hallmark of cancer of the nasopharynx is the missed diagnosis. In case after case the patient comes to the physician with salient symptoms calling for examination and biopsy of the nasopharynx, only to be put off for weeks or months with inappropriate treatment or operations. These are the outstanding facts which emerged from this study. Here are three glaring examples:

1. A man, aged 61 years, consulted his physician because of increasing deafness in the left ear. He was allegedly told that it was due to otosclerosis. The following month he had pain in the left upper jaw. He consulted his dentist who extracted a tooth, but the pain persisted. Later that month he noted obstruction of the left nasal passage. He was told that he had a deviated nasal septum, and a submucous resection was performed. His symptoms continued. Another oral surgeon was consulted and a second tooth was removed without relief. Finally, five months after onset of symptoms, the patient consulted an otolaryngologist who, for the first time, examined the nasopharynx, and performed a biopsy of the lesion.

2. A housewife, aged 55 years, noted swelling in the right side of the neck. She consulted a physician who treated her with penicillin for three months. The woman noted no improvement and sought admission to a hospital. A biopsy of the right *arytenoid* was reported as negative. The nasopharynx was not examined. She experienced numbness of the left side of the face, headache, and diplopia. For six months nothing was done. Finally she was admitted to the neurological service of The Mount Sinai Hospital. By this time, there was involvement of the left IIIrd, IVth, and Vth, bilateral VIth, and left VIIth cranial nerves. She was thought to have brain stem disease. An otolaryngological consultation revealed diffuse fullness of the pos-

terior wall and left lateral recess of the nasopharynx, with scattered lymphoid follicles covered by intact mucosa. Biopsy revealed embryonal cell carcinoma.

3. A man, aged 54 years, noted pain in the left ear. He was seen by a local physician and referred to an otolaryngologist who reported no disease. The nasopharynx was not examined. Two weeks later, the patient noted diplopia while driving his automobile. He consulted an ophthalmologist who noted weakness of the left abducens. This was attributed to a viral infection. After another three weeks he felt numbness of the left side of the face. He was hospitalized for three weeks and was seen by a number of physicians, including a neurologist, but no one examined the nasopharynx. He sought admission to another hospital where he remained yet another two weeks. Finally he consulted a neurosurgeon who found involvement of the motor and sensory divisions of the left Vth nerve, left VIth nerve, left conductive hearing impairment, and nystagmus on right lateral gaze. For the first time, three months after onset, the nasopharynx was suspected as the source of disease. However, on the initial examination by an otolaryngologist only a slight fullness of the posterior wall was seen. Biopsy was reported negative. A left carotid angiogram was reported as normal. Roentgenogram of the skull revealed some destruction along the base on the left side involving the medial aspect of the middle cranial fossa. An enlarged lymph node was discovered and biopsy reported embryonal cell carcinoma. Reexamination of the nasopharynx revealed a lesion in the left lateral recess. There was a lapse of three and one-half months from the first symptom to the positive diagnosis.

Analysis of the records in this series reveals errors in at least 68 of 90 cases. Most of the errors resulted from failure on the part of the treating physician to consider the diagnosis. The clinical diagnosis was variously listed as cervical adenitis, nasal polyposis, deviated nasal septum, sinusitis, pharyngitis, tonsillitis, adenoiditis, orbital tumor, trigeminal neuralgia, brain stem disease, myasthenia gravis, and otosclerosis. Fourteen of the original biopsies of the nasopharynx were negative; it was only on the second or third biopsy that a positive diagnosis was obtained. In many cases histopathology was incorrectly reported as benign lymphoid hyperplasia, chronic inflammation, giant follicular lymphoblastoma, Hodgkin's disease, squamous cell carcinoma, or transitional cell carcinoma.

There were unnecessary adenoidectomies and tonsillectomies, submucous resections, and Caldwell-Luc operations. In 18 cases nasopharyngeal examinations were undertaken only after lymph node biopsy revealed embryonal cell carcinoma.

Treatment

The present method of treatment is based on combined therapy. Super-voltage radiotherapy, using Co⁶⁰ is administered over a period of 5 to 6 weeks. A tumor dose, ranging from 5000 r for embryonal cell carcinoma, through 5500 r for immature squamous cell carcinoma, to 6000 r for mature

squamous cell carcinoma, is given. Radiation therapy is also administered to cervical metastases (2, 7j, 17).

It has been found that in most cases the cervical metastases respond to irradiation, but recur after 6 to 8 months. Therefore, from 3 to 6 weeks after radiotherapy, biopsy of the nasopharynx and radiographic examinations of the skull and chest are repeated; and if negative, radical neck dissection is performed on the affected side. Frequent complete physical examinations are done to detect distant metastases. Chemotherapy was used in 12 refractory cases; there was some palliation but there were no cures (7k, 18).

Results of Treatment

Eighty-three patients were treated by radiotherapy: 47 had orthovoltage alone; 20 had Co⁶⁰ teletherapy; and 16 had radical neck dissection in addition. The five-year survival rate for orthovoltage alone was 28%; for Co⁶⁰ alone, 15%; and for Co⁶⁰ combined with neck dissection, 31%. It should be noted that the rate for orthovoltage is definitive, but the rates for Co⁶⁰ and radical neck dissection may improve when the five-year period of observation is completed (four cases). As to mortality rates, for orthovoltage alone, it was 68%; for Co⁶⁰, 50%; and for radical neck dissection, 37%. There are three cases of persistent disease. Seven patients were not suitable for treatment. Orthovoltage was used in the early cases; supervoltage has been employed since 1959. Since 1958 radical neck dissections have been done with increasing frequency. Of 16 patients who had the operation performed, 6, or 37%, have survived over five years free of disease. The nodes were positive for cancer in 12 cases, or 75%.

In the first decade (1935–1944) of this study, the survival rate was 20% (3 of 15 patients); in the second decade (1945–1954), 25% (8 of 32); and in the third decade (1955–1964), 30% (11 of 36).

When the results of treatment were analyzed according to the cellular nature of the tumor, noteworthy differences became apparent.

1. The embryonal cell carcinoma, or Schmincke tumor, comprised 50 cases. Of these, there were 16 patients surviving over five years with no evidence of disease, including one patient who survived without evidence of disease for 15 years, and died at the age of 79 from pulmonary emphysema. Six survivors were in Stage I, eight were in Stage II, and two were in Stage III when first seen. Case 1 in this series was admitted to The Mount Sinai Hospital in 1935. A radical neck dissection was performed by the general surgeons. Following the report of embryonal cell carcinoma in the cervical lymph nodes, the nasopharynx was examined and the lesion was discovered. The nasopharynx was irradiated by orthovoltage. The patient has remained well for 33 years. Of two cases in Stage III one patient had unilateral amblyopia, proptosis, and ophthalmoplegia. He had been referred for an orbital exenteration, but the ophthalmologist suspected the possibility of a nasopharyngeal tumor. Examination revealed only some fullness in the left

lateral recess; there was no visible lesion. Biopsy of the nasopharynx revealed embryonal cell carcinoma, and the patient has remained well nine years after cobalt⁶⁰ teletherapy. The second patient with cranial nerve involvement was treated originally by orthovoltage. He suffered from recurrent disease in the neck, which was treated by radium implantation, a radical neck dissection, and cobalt irradiation. There is no evidence of disease for eight years.

Four cases were lost to follow-up. Of two additional cases admitted within the past five years with persistent disease, one had a neck dissection. Of the deaths, 3 were in Stage I, 6 in Stage II, and 16 in Stage III when first seen. Sixteen patients had orthovoltage and six had cobalt. Three had radical neck dissection in addition.

Summary of the embryonal cell carcinomas: Survival over five years: 16 of 50, or 32%; under five years: 3 of 50, or 6%. Mortality from other causes, 1; mortality from disease, 25 of 50, or 50%. Four of 50, or 8%, were lost to follow-up. Two of 50, or 4%, have persistent disease.

2. Immature squamous cell carcinomas comprised 25 cases. There were only four, or 16%, who survived over five years without evidence of disease. Two were in Stage I; two, in Stage II when first seen. Of these survivals, three patients had radical neck dissection after cobalt therapy. The nodes were positive in two cases. One additional patient is alive and well after four years. One patient was treated with orthovoltage and a neck dissection, but died one day postoperatively from cardiac failure. A second patient died from injuries suffered in an assault two years after therapy. Sixteen patients died of the disease: 5 were in Stage II; 11 in Stage III on initial examination. Of the latter, two patients had radical neck dissection following cobalt therapy. Three patients were not treated. Two patients were lost to follow-up.

Summary of immature squamous cell carcinomas: Survival over five years: 4 of 25, or 16%; under five years: 1, or 4%. Mortality due to other causes: 2, or 8%; due to disease: 16 of 25, or 64%. Two patients, or 8%, were lost to follow-up.

3. There were seven cases of mature squamous cell carcinoma. All were in Stage III on admission; there were no survivors.

4. In two cases the diagnosis was unclassified carcinoma. One patient in Stage II showed no evidence of disease in the nasopharynx or neck for 19 years following radiotherapy. However, 12 years after therapy to the nasopharynx a scirrhus carcinoma of the breast developed, and seven years later she died of carcinoma of the esophagus. The second patient died early in the disease.

5. Sarcomas were relatively infrequent; there were only six cases. There were four cases of lymphosarcoma. One is living free of disease 19 years after therapy; three have died. One case of angiofibrosarcoma in a 13-year-old girl was fatal in seven weeks. One case of angiosarcoma with persistent disease in the cervical lymph nodes had the original lesion in the tongue four years previously.

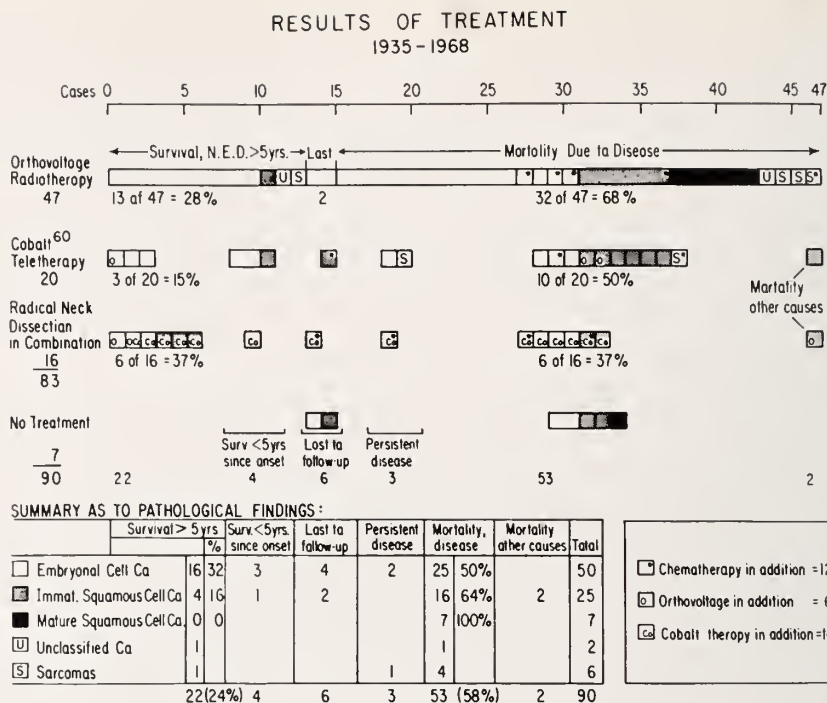


Chart 9.

Summary of sarcomas: Survival; one case. Persistent disease; one case. Mortality; 4 of 6, or 67% (see Chart 9).

Recurrences

There were 30 instances of recurrent disease in the first two years after treatment. Four cases occurred between the third and fifth years, 3 in the seventh, and 2 in the ninth year. Most of the recurrences were metastases to the cervical lymph nodes; only 5 cases were in the nasopharynx; 10 involved the cranial nerves. Distant metastases in 18 cases to the liver, lungs, and bones were usually accompanied by disease in the cervical and mediastinal nodes.

There were 2 cases of radionecrosis of the maxilla, and 4 cases involving the external auditory canal. The lesions were relatively mild and healed eventually. Incidentally, 4 patients had unrelated carcinomas elsewhere during the course of observation.

Conclusions

1. The cellular type of the tumor is the most significant prognostic factor in cancer of the nasopharynx. The five-year survival rate for embryonal cell carcinoma is 32%; for immature squamous cell carcinoma, 16%; and for mature squamous cell carcinoma, 0%.

2. The stage of disease is the second important factor in the prognosis. The five-year survival rate in Stage I is 53%; Stage II, 34%; and Stage III, 5%.

3. The etiology remains unknown. There is a marked racial predilection in Chinese. A genetic factor may prove to be the key.

4. The missed diagnosis is the tragic hallmark of this disease.

5. Employment of radical neck dissection in combination with radiotherapy resulted in a five-year survival rate of 37%.

Acknowledgments

Part of the work presented here was submitted originally as a candidate's thesis to the American Laryngological, Rhinological and Otological Society in 1960, and was published in *The Laryngoscope* in October 1961. Portions of the text and illustrations are reprinted through the courtesy of the Triological Society and the editor of *The Laryngoscope*.

This paper is dedicated to the memory of Dr. Sadao Otani, who died on March 7, 1969. Dr. Otani's diligent instruction in pathology, patient review of the microscopic slides, and classification of the pathological material contributed immeasurably to this study.

I express my appreciation to the following: Doctors Joseph L. Goldman, John Boland, Sidney M. Silverstone, Ezra M. Greenspan, Mack Fieber, Eric J. Cassell, Morris B. Bender, Sidney W. Gross, Morris Feldstein, Willy Mautner, Mamoru Kaneko, Cyril Toker, and Messrs. Bruno Hein and Paul J. Singh-Roy. Also thanks for permission to include clinical material are due to the following: Doctors Morris S. Bender, Joseph G. Druss, Harry Rosenwasser, Louis Kleinfeld, Eugene R. Snyder, Max L. Som, Vernon A. Weinstein, Eugene W. Friedman, Leon Arnold, Sidney S. Feuerstein, A. Albert Cohen, George M. Sappol and the late Poon L. Lim.

References

1. Godtfredsen, E.: Ophthalmologic and Neurologic Symptoms at Malignant Nasopharyngeal Tumors, Munksgaard, Copenhagen, *Acta Ophthal Suppl* 22, pp 1-323, 1944.
2. Lederman, M.: *Cancer of the Nasopharynx*, Charles C Thomas, Springfield, Ill., 1961.
3. Schmincke, A.: Über Lympho-epitheliale Geschwülste, *Beitr z path, Anat allg Path* 68:161-170, 1921.
4. Regaud, C., and Reverchon, L.: Sur un Cas d'Epithelioma Epidermoide Developpe dans le Massif Maxillaire Superieur, Étendu aux Teguments de la Face, aux Cavites Buccale, Nasale et Orbitaire, Ainsi qu' aux Ganglions du Cou, Gueri par la Curietherapie, *Rev Laryng (Bordeaux)* 42:369-378, 1921.
5. Saphir, O.: *A Text on Systemic Pathology*, Grune & Stratton, New York and London, 1959, pp 1057-1079.
6. Digby, K. H., Fook, W. L., and Che, Y. T.: Nasopharyngeal Malignancy, *Brit J Surg* 28:517-537, 1941.
7. Muir, C. S., and Shanmugaratnam, K., Edit.: *Cancer of the Nasopharynx*, UICC Monograph Series, Medical Examination Publishing Co., Flushing, New York, Vol. 1, 1967.
 - a. Ali, M. Y.: Distribution and Character of the Squamous Epithelium in the Human Nasopharynx, 1:138-146.
 - b. Yeh, S.: Histopathology of Nasopharyngeal Cancer, 1:147-152.
 - c. Shanmugaratnam, K. and Muir, C. S.: Nasopharyngeal Carcinoma, Origin and Structure, 1:153-162.

- d. Svoboda, D. J., Kirchner, F. R., and Shanmugaratnam, K.: The Fine Structure of Nasopharyngeal Carcinomas, 1:163-171.
- e. Muir, C. S.: Nasopharyngeal Cancer—A Historical Vignette, 1:13-17.
- f. Ho, H. C.: Nasopharyngeal Carcinoma in Hong Kong, 1:58-63.
- g. Bailar, J. C. III: Nasopharyngeal Cancer in White Populations—a World-Wide Survey, 1:18-23.
- h. Bailar, J. C. III: Race, Environment, and Family in the Epidemiology of Cancer of the Nasopharynx, 1:101-105.
- i. Ho, H. C.: Radiological Diagnosis of Nasopharyngeal Carcinoma with Special Reference to its Spread through the Base of the Skull, 1:238-245.
- j. Chia, K. B.: Radiotherapy in Treatment of Carcinoma of the Nasopharynx, 1:218-221.
- k. Harrison, D. F. N.: The Role of Chemotherapy in the Management of Advanced Neoplasms of the Nasopharynx and Paranasal Sinuses, 1:229-237.
8. Geist, R. M., and Portmann, U. V.: Primary Malignant Tumors of the Nasopharynx, *Amer J Roentgen* 68:262-271, 1952.
9. Sturton, S. D., Wen, H. L., and Sturton, O. G.: Etiology of Cancer of Nasopharynx, *Cancer* 19:1666-1669, 1966.
10. Pang, L. Q.: Carcinoma of Nasopharynx, *Ann Otol* 68:356-371, 1959.
11. Pang, L. Q.: Carcinoma of Nasopharynx: Experience with 66 Patients, *Arch Otolaryng* 82:622-628, 1965.
12. Buell, P.: Nasopharyngeal Cancer in Chinese of California, *Brit J Cancer* 19:459-470, 1965.
13. Jung, P. F.: Familial Tendency of Nasopharyngeal Carcinoma, *Pacif Med Surg* 73:242-243, 1965.
14. Baclesse, F.: Les Cancers du Rhinopharynx: Étude Radiographique, Resultats Éloignés par la Radiotherapie, Paris, *Ann Otolaryng* 73:509-520, 1956.
15. Chakravorty, R. A., and Ewing, M. R.: Nasopharyngeal Cancer: Problem in Diagnosis, *Brit J Surg* 44:388-393, 1957.
16. Simmons, M. W., and Ariel, I. M.: Carcinoma of the Nasopharynx, *Surg Gynec Obstet* 88:763-775, 1949.
17. Lenz, M.: Malignant Neoplasm of the Nose, Nasopharynx, and Paranasal Sinuses: Evaluation of Radiotherapy, *Trans Amer Acad Ophthal Otolaryng* 55:214-225, 1951.
18. Greenspan, E. M.: Thio-TEPA and Methotrexate Chemotherapy of Advanced Ovarian Carcinoma, *J Mount Sinai Hosp NY* 35(1):52-67, 1968.

Received for publication January 7, 1969

Hemangioma as a Cause of Cryptogenic Gastrointestinal Hemorrhage

JOSE C. CACATIAN, M.D.† AND MILTON KANNERSTEIN, M.D.‡

Hemangioma of the gastrointestinal tract is a relatively uncommon lesion, but not so exceedingly rare that it can be discounted as a cause of cryptogenic bleeding. Moreover, death or protracted disability resulting from anemia may be prevented by appropriate and timely surgery. A case of hemangioma of the ileum with anemia unexplained for many years and subsequently, with detection of melena, erroneously attributed to a duodenal ulcer, was recently encountered in this hospital and treated successfully.

Case Report

A 28-year-old white housewife and registered nurse was admitted to the Barnert Memorial Hospital Center with severe anemia. For about a month prior to admission she had been having episodes of nausea, nervousness, light-headedness, palpitations, and dyspnea on exertion. The anemia had appeared in childhood, gradually becoming more pronounced. Its cause remained undiscovered. She experienced the usual childhood diseases and pneumonia on one occasion. She had had no known exposure to toxic substances. At the age of 17 she experienced the first recognized episode of gastrointestinal hemorrhage, severe enough to require transfusion of three units of blood. At that time, she was treated in another hospital where a diagnosis of duodenal ulcer was made on the basis of a gastrointestinal x-ray series. Bleeding recurred once each year during the next two years and again four years later, but blood transfusion was not required. On the last occasion, x-ray studies again suggested a duodenal ulcer, but the findings were considered equivocal. There were no abdominal symptoms at any time. During the five years before the present admission there had been no recognized episode of gastrointestinal bleeding, but the anemia persisted and became increasingly severe. Two years before this admission she underwent a uterine curettage in another hospital for menometrorrhagia. Subsequently her menstrual function was normal and regular. She had three normal pregnancies and deliveries at term.

The family history was not contributory. There was no relative with known anemia, bleeding tendencies, or hemangioma.

Physical examination revealed no significant feature other than pro-

From the Department of Pathology, Barnert Memorial Hospital Center, Paterson, New Jersey.

† Formerly Resident in Pathology, Barnert Memorial Hospital Center, Paterson, N.J.

‡ Assistant Clinical Professor of Pathology, the Mount Sinai School of Medicine, New York, N.Y.

Reprint Requests to Dr. M. Kannerstein, Barnert Memorial Hospital Center, Paterson, New Jersey 07514.



FIG. 1. Posteroanterior abdominal film showing a loop of distal ileum with numerous indentations on its inferior border suggesting a mucosal or submucosal tumor.

nounced pallor. The blood pressure was 126/64 mm Hg; pulse 88 beats per minute; respirations 20 per minute; and temperature 99.6°F (37.6°C). There were no hemangiomas of the skin or visible mucous membranes.

Hematologic study showed hypochromic anemia, with slight anisocytosis and polychromatophilia. On admission, the hemoglobin was 5.5 gm/100 ml, the red blood cell count (RBC) 2,510,000/cu mm with 4.1% reticulocytes, and a hematocrit of 20%. The white blood cell count (WBC) and differential count were normal. The number of platelets was adequate. A bone marrow needle biopsy showed normal cellularity and megakaryocytic representation, with orderly maturation. There was a decrease of hemosiderin. The stools were consistently positive for occult blood. All other laboratory examinations, including direct and indirect Coomb's tests, serum bilirubin level, and total protein and albumin/globulin ratio, gave normal values.

Chest x-ray findings were normal. X-ray studies of the colon by barium and a contrast media showed no abnormality. An upper gastrointestinal



FIG. 2. Enlarged spot-film: The indentations in detail suggesting a submucosal location of the lesion.

series disclosed no pathologic feature. In particular, there was no evidence of duodenal ulcer. A small bowel x-ray study revealed an abnormal loop of distal ileum (Figs. 1 and 2).

The patient was placed on Imferon®, 2 cc intramuscularly, for a few days. A spiking fever for several days required antibiotic treatment. She received blood transfusions, one unit per day, for three days after subsidence of the fever. On the 13th hospital day, when her hemoglobin had reached 12.0 gm/100 ml, she was subjected to abdominal exploration with a preoperative diagnosis of "small bowel tumor."

Examination of the small bowel disclosed a purplish-red vascular mass in the midileum. The mass involved 5 cm of bowel and almost completely encircled it. It was nonpulsatile and collapsed after resection. There was no similar lesion elsewhere in the gastrointestinal tract. Inspection and palpation of the duodenal bulb did not reveal evidence of a peptic ulcer. A soft purple elevation was present in the anterior surface of the liver. Fifteen centimeters of ileum, containing the mass, were resected and an end-to-end anastomosis was performed. The hepatic lesion was not resected.

The postoperative course was uneventful. No additional blood transfusion was necessary. The hemoglobin level remained at 11.5 gm. The patient was discharged from the hospital a week after operation. During the follow-up period her stools became negative for occult blood. Her hemoglobin three



Fig. 3. Serosal aspect of segment of ileum showing elevated vascular area.

months after operation was 13.0 gm per 100 ml, without further treatment for anemia.

Pathological examination of the specimen was as follows: The specimen consisted of a segment of small intestine with attached mesentery. It measured 15 cm in length and 4.5 cm in average circumference. In the approximate midportion, on the serosal surface, was a fairly sharply delineated, elevated, granular purplish-red, obviously vascular area measuring 5 x 3 cm in greatest diameter (Fig. 3). The lesion lay on the antimesenteric aspect and extended around toward the mesenteric border on each side. Corresponding to this area the mucosa showed a bluish discoloration. Its center in the long axis was depressed (Fig. 4). On section, blood escaped from the lesion with collapse of the distended serosal vessels. The entire thickness of the wall grossly appeared involved.

Microscopic examination disclosed, through the thickness of the intestinal wall, large blood-filled, endothelium-lined spaces with hypocellular thick collagenous walls (Fig. 5). The vascular spaces were present in all layers, replacing the normal components of the wall, extending into the mucosa. One of the mucosal vascular spaces contained an organizing thrombus. The pathologic diagnosis was cavernous hemangioma of the ileum.

Comment

Hemangiomas have been found to occur singly and in groups from the oral cavity to the anus. Multiple lesions may be present along the entire gastrointestinal tract. In a significant number of cases there are coexisting he-

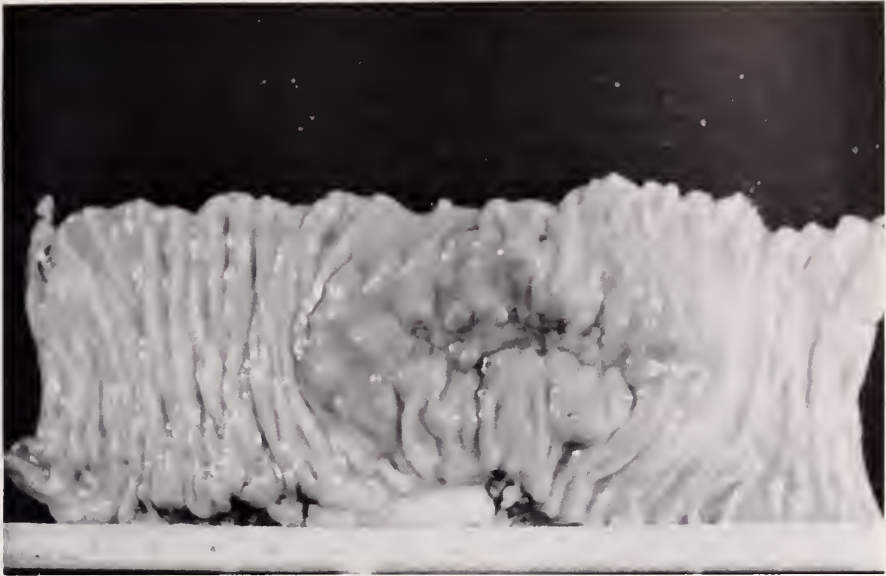


FIG. 4. Mucosal aspect of involved ileum. In the central portion the mucosal pattern is distorted, the mucosa elevated with an axial midline depression. It had a bluish color.

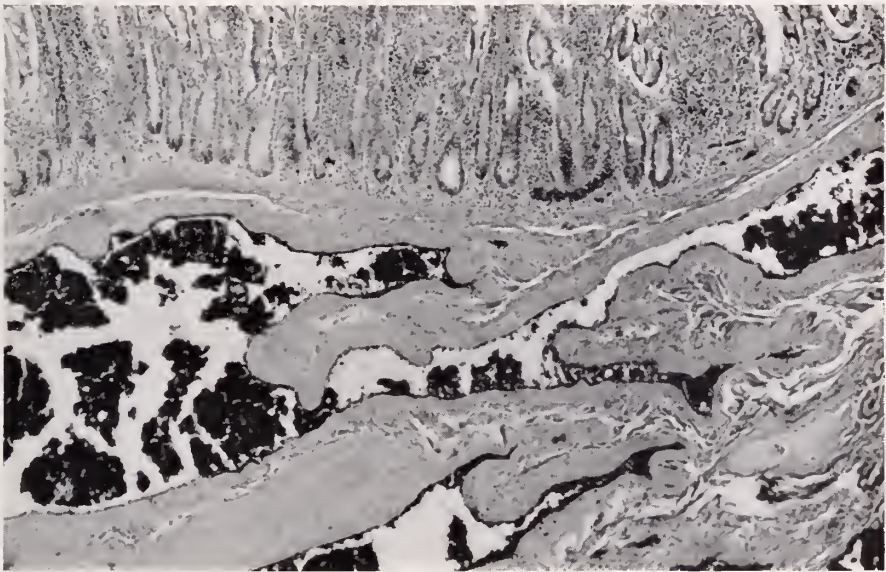


FIG. 5. Photomicrograph showing typical cavernous hemangioma in submucosa. In other areas all the layers were involved (H & E, $\times 125$).

mangiomas in other viscera and in the skin. The first report of a gastrointestinal hemangioma was made in 1838 by Phillips (1). The patient had rectal hemorrhages which began when he was 18 years old. He was found to have an "erectile tumor," evidently a cavernous hemangioma, within the anal canal.

After ligation the lesion sloughed off without further hemorrhage, and there was no recurrence.

In 1936 Kaijser (2) was able to find 74 cases in the world literature, and added two. One was that of an 8-year-old boy with rectal hemorrhage and anemia from the time he was two. He had an unsuspected cavernous hemangioma of the sigmoid colon which was eventually resected with recovery. The other patient was a 19-year-old girl with recurrent severe anemia, hematemesis, and melena from the age of four. Hemangiomas were present in her lips, tongue, and axilla. On abdominal exploration, an inoperable diffuse, infiltrating, cavernous hemangioma was found in the esophagus and stomach.

Vascular lesions of the gastrointestinal tract may be of benign or malignant character. The latter are a small minority of the total. Gentry, Dockerty, and Clagget (3) in 1949, collected 234 cases of vascular lesions from the literature, only of which 45 (14.5%) were malignant. From the files of the Mayo Clinic they obtained 106 cases, of which 14 (13.2%) were malignant. Of the malignant tumors in their series, half were in the stomach, whereas only 4 of the benign lesions were located there. Three of the malignant lesions, and 59 of the benign, were in the small intestine.

The pathogenesis of hemangiomas is not clearly defined. It is generally agreed that most of them are congenital, but it is uncertain whether they should be considered true neoplasms or malformations. Some writers regard them as hamartomas.

Hemangiomas vary in structure. The type, as well as the location and extent of the lesion, appears to have some bearing on its clinical course. The classification originated by Oberndorfer (4), but often attributed to Kaijser since his classic report, has been widely used. In his classification there are four types of hemangiomas.

Gentry and his co-workers later presented a somewhat more elaborate and refined classification, which also separates malignant vascular lesions from the benign hemangiomata with which we are concerned here. For further details the reader is referred to the papers of Kaijser and Gentry, et al.

Hemangiomas of the gastrointestinal tract may exist without causing symptoms at any time during the life of the patient (3). Many are discovered only accidentally at autopsy or during abdominal operations for other conditions. When they produce signs and symptoms their presence is most often unsuspected because of their rarity, and they are usually mistaken for the more common conditions with similar symptomatology. The most frequent presenting sign is gastrointestinal bleeding which may be occult and go on for years causing a cryptogenic anemia, or it may be so massive as to require immediate surgical intervention. The diffuse or expansive type of hemangioma is more apt to bleed, starting in early life. It may produce obstruction; however, obstruction is much less frequent than bleeding and may also be caused by a polypoid tumor or encroachment of a proliferating capillary hemangioma on the bowel lumen, or may be the result of intussusception.

Ackerman (5) reported a fatal case of cavernous hemangioma of the duodenum rupturing retroperitoneally. The tumor may also become the seat of inflammation, so that it may simulate appendicitis, if situated in the terminal ileum.

The preoperative diagnosis of gastrointestinal tract hemangiomas is exceedingly difficult, except when the lesions are visible by endoscopy. There are, however, certain suggestive signs which should enable one at least to suspect the presence of such tumors. Kaijser had recognized the frequent occurrence of phleboliths in the cavernous type of hemangiomas. In 1959, Rissier (6) stated that this finding alone suggested the possibility of hemangioma, especially if they occur grouped or outside the pelvic area. If the phleboliths are present in a filling defect, the diagnosis is virtually assured. He cited four cases from the literature that were correctly diagnosed preoperatively on the basis of this finding. The presence of even a single hemangioma in the external body surfaces, should also make one strongly suspicious that a similar lesion may be the cause of cryptogenic gastrointestinal bleeding. It is well recognized that intussusception of the small intestine in the adult is usually caused by a benign neoplasm which may be a hemangioma. This lesion in Raiford's large series of small intestinal benign neoplasms was the fourth most common (7). Lastly, in all cases of obscure gastrointestinal bleeding at any age, this condition should always be considered in the differential diagnosis. In summary, the diagnosis should usually be made, as Ackerman stated, "in the presence of visible hemangiomata, obscure hemorrhage, and signs of acute or chronic obstruction, together with x-ray findings suggestive of this condition."

The decision regarding the treatment of these lesions should depend on their location, extent, and their association with other intraperitoneal structures. Surgical resection, if feasible, is the treatment of choice. Adequate preoperative preparation of the patient is, of course, necessary. For lesions that are too extensive for adequate resection, palliative forms of treatment, including cauterization, partial extirpation, roentgen therapy, and sclerosing injections should be considered.

The case presented here was of the single, diffuse expansive type, according to the classification of Gentry, et al. The history of an unexplained anemia is classical. The attribution of the anemia to a bleeding duodenal ulcer was based on dubious grounds. Bleeding continued in occult fashion between and after the recognized episodes. Only a specific x-ray study of the small bowel, by disclosing abnormalities, led to exploratory laparotomy and resection of the lesion. In the absence of this localizing finding, the reluctance of a surgeon to explore, despite the evidence of blood loss from the gastrointestinal tract, is easy to understand. A small mucosal lesion of many varieties is often impossible to locate at surgery if there has been no prior x-ray demonstration. In fact, difficulty in finding the lesion in the excised specimen is not unusual. Bongiovi and Duffy (8) have recently described a case of a very minute gastric hemangioma limited to the mucosa and sub-

mucosa, associated with severe anemia. If hemorrhage had been massive enough in the present case to be life-threatening, and the intestinal lesion had not been detected by x-ray for one reason or another, one might have been led by the history of an earlier diagnosis of a duodenal ulcer into performing a perfectly futile "blind" gastrectomy.

The lesion here may be presumed to be "congenital," that is to have existed throughout life, gradually enlarging, involving the mucosa with episodes of ulceration and hemorrhage.

The interest in this case lies in emphasizing the alertness and persistence required of the physician in pursuing the diagnosis of etiologically obscure or atypical gastrointestinal bleeding (9).

Summary

A patient with protracted cryptogenic gastrointestinal bleeding and consequent severe anemia was demonstrated at laparotomy to have a cavernous hemangioma of the ileum. A probably illusory diagnosis of peptic ulcer over a period of many years had prevented correct evaluation of the case, and denied the patient proper therapy.

A review of reported cases indicates that vascular lesions of the gastrointestinal tract may manifest themselves at any age. The characteristic presenting feature is hemorrhage. This may be occult, in which case anemia is the first, or overt finding. Minute size, even with disproportionately massive hemorrhage, may make localization as difficult as diagnosis. Large size and multiplicity of lesions produce their own problems in management. Obstruction and perforation of the bowel are occasional complications. A roentgenographic feature of occasional diagnostic assistance, especially in cavernous hemangiomas, is the presence of phleboliths. Since curative surgical extirpation is quite feasible in many cases, the existence and significance of these lesions must be kept in mind.

Acknowledgments

We wish to thank Doctors S. Jaslow and P. Shapiro for the use of the clinical material, and Doctors S. Bluestein and C. Zimmerman who have previously presented the roentgenologic findings.

References

1. Phillips, B.: Erectile Tumor of the Anus, London Medical Gazette 1:514, 1839. (Cited by Gentry et al, Reference 3).
2. Kaijser, R.: Über Hämangiome des Tractus Gastro-Intestinalis, Arch Klin Chir 187: 351-388, 1936.
3. Gentry, R. W., Dockerty, M. B., and Claggett, O. T.: Vascular Malformations and Tumors of the Gastrointestinal Tract, Int Abstr Surg 88:281-323, 1949.
4. Oberndorfer, S.: Hämangiome, In *Handbuch der speziellen pathologischen Anatomie und Histologie*, Henke, F. und Lubarsch, O., eds. 4:741, Julius Springer, Berlin, 1929.

5. Ackerman, L. V.: Cavernous Hemangiomas of the Small and Large Bowel, *Amer J Cancer* 30:753-757, 1937.
6. Rissier, H. L., Jr.: Hemangiomatosis of the Intestine, *Gastroenterologia* 93:357-385, 1960.
7. Raiford, T. S.: Tumors of the Small Intestine, *Arch Surg* 25:122, 1932.
8. Bongiovi, J. J., Jr., and Duffy, J. L.: Gastric Hemangioma Associated with Upper Gastrointestinal Bleeding, *Arch Surg* 95:93-98, 1967.
9. Bernstein, J. S., and Woo Yoon Chey: Small Bowel Tumors. A Clinical Study of 109 Cases, *J Mount Sinai Hosp NY* 25:1-28, 1958.
10. Bluestein, S. G., and Zimmerman, C.: Radiologic Notes, *J Mount Sinai Hosp NY* 34: 540-543, 1967.

Received for publication November 18, 1968

Acute Appendicitis Presenting as Multiple, Extra-Abdominal Abscesses

STEPHEN A. GELLER, M.D.*

Complications of acute appendicitis have become relatively infrequent with the almost universal availability of antibiotics, and death is most unusual. Once perforation of the acutely inflamed appendix does occur, however, mortality and morbidity become serious clinical problems. The incidence of perforation, of subsequent sequelae, and of mortality all reach a peak in the aged (1).

The medical and surgical services of The Mount Sinai Hospital recently had the opportunity of caring for an elderly man who presented with, and eventually died of, some unusual sequelae of perforated appendicitis.

Case Report

A 68-year-old man came to the emergency room complaining of chest pain, and after physical and x-ray examination, was found to have a right pleural effusion.

He first became aware of right anterior chest pain, accentuated by respiration, one week prior to admission. The pain continued and he had several shaking chills, alternating with sensations of fever, but without night sweats. Three days prior to admission, a private physician advised him that he had pneumonia and gave a single intramuscular injection of penicillin, as well as an oral antibiotic, which the patient took up to the time of hospitalization. Following that examination, a cough productive of thick, yellow sputum ensued, with subsequent reduction of pleuritic pain and increase of appetite.

The patient had had three prior episodes of pneumonia many years ago, and was a heavy cigarette smoker. A native of Puerto Rico, he had been in New York City for the last 49 years, and was employed as a janitor. He admitted to heavy intake of alcohol up to five years ago.

He had been constipated at the time of onset of symptoms. He noted occasional fatty food intolerance and had had a left inguinal hernia for two years, and a right inguinal hernia for three months, with mild discomfort on the right side. He experienced nocturia and some difficulty in voiding.

Examination revealed a thin, elderly, neglected-appearing male in no acute distress. His temperature was 101.2°F, with a blood pressure of 120/70, a regular pulse rate of 88/min, and a respiratory rate of 24/min. Poor expansion of the chest was noted, with mild intercostal retractions, most marked

* Instructor, Department of Pathology, the Mount Sinai School of Medicine of the City University of New York, N.Y.

Reprints: Stephen A. Geller, M.D., U.S. Naval Hospital, Beaufort, South Carolina 29902.

on the right side. Dullness was easily percussed at the right base posteriorly, and decreased breath sounds were accompanied by coarse rhonchi and scattered rales.

The abdomen was mildly distended, and somewhat tense. A vague sensation of fullness and mild tenderness was elicited by deep palpation of the right lower quadrant. Inguinal herniae were present, with the right side difficult to reduce. The prostate gland was moderately enlarged and nodular. The remainder of the physical examination was within normal limits.

Hemoglobin on admission was 14.9 gm per 100 ml. The white blood cell count was 8,150 cells/mm³, with a slight shift to the left. Sedimentation rate was 76 mm/hr; serum glucose was 180 mg per 100 ml; and the total protein was 6.0 gm per 100 ml, with an albumin of 2.5 gm per 100 ml. The remaining laboratory determination, including that for blood urea nitrogen, creatinine, uric acid, chlorides, potassium, sodium, calcium, bilirubin, cholesterol, alkaline and acid phosphatase, and serum glutamic and oxalic transaminase, produced findings within normal limits. The Quick one-stage prothrombin time was 15.5 seconds, with a control of 13 seconds. Serologic tests for syphilis were negative.

Three hundred cubic centimeters of serosanguinous pleural fluid, with a specific gravity of 1.020, was aspirated from the right thoracic cavity. This contained approximately 10,000 red and 18,000 white blood cells per mm³. More than 90 percent of the white cells were polymorphonuclear leukocytes. Smears prepared from this fluid were negative for bacteria and acid-fast organisms, and a cell block revealed only large numbers of mesothelial and acute inflammatory cells.

Therapy with intramuscular penicillin was continued because of elevated temperatures to 103°F. First strength PPD test gave negative results.

The temperature transiently dropped to 100°F, then suddenly rose to 102.8°F when the patient complained of groin tenderness. The right scrotum was warm, red, markedly enlarged, tender, and there was a small, black eschar on its inferior aspect. The right epididymis was thick and hard, and both testicles were slightly tender.

The right scrotal abscess was incised and a foul-smelling, brown exudate was drained. Bacterial culture of this fluid revealed *Escherichia coli*. Culture of blood, performed at this time, was sterile.

Chloromycetin was added to the therapeutic regimen and the previous incision was extended to more adequately drain the scrotal abscess. A right orchiectomy was performed. The immediate postoperative course was satisfactory, with a temperature of 100°F. The cellulitis of the groin, however, extended to the flank and the medial aspect of the right thigh. White blood cell count at this time was 11,200 cells/mm³, with a marked shift to the left.

Urinary output was maintained and Keflin therapy was begun; however, the cellulitis continued to extend to the flank and onto the right abdominal wall. Although the temperature remained at 102.8°F, the cellulitis appeared to be improving by the eighth hospital day. The chest x-ray remained essentially unchanged and an attempted diagnostic thoracentesis was unsuccessful.

The temperature fell to 99.6°F when the patient began to expectorate copious amounts of purulent, blood-streaked sputum. Many gram-positive cocci, in groups and chains, as well as large gram-negative rods, were demonstrated. The white blood cell count rose to 21,000 cells/mm³.

The posterior base of the right hemithorax was flat to percussion, and wet rales, and succussion splash were heard. A homogenous right lower lobe density, with a 3.0 cm ovoid, radiolucent shadow containing an air-fluid level, was seen on chest x-ray examination. Left hilar pneumonitis was also noted.

Following this, the patient was disoriented, with echolalia and perservation. Physical examination of the central nervous system failed to demonstrate a focal lesion, and lumbar puncture revealed an opening pressure of 140 mm Hg, and a crystal clear, colorless, sterile cerebrospinal fluid was easily obtained.

Closed thoracotomy was performed late on the tenth day, with insertion of a drainage tube. Bacterial culture of the small amount of blood stained exudate revealed *Escherichia coli* and *Enterococcus* species. Continued spreading of the cellulitis at the right flank necessitated incision and drainage. A large, multiloculated fascial cavity, containing thick, bloody exudate, extended anteriorly to the suprapubic area, and posteriorly, on the flank, to the mid-axillary line.

Following these procedures the patient had repeated convulsive seizures. His pulse was rapid and faint, and the hematocrit was 24 percent. Measures to combat gram-negative shock, including the infusion of four units of whole blood and administration of intravenous Solu-Cortef®, intramuscular Neomycin®, and 30,000,000 units of penicillin given parenterally, were instituted. Tracheostomy was performed and slight clinical improvement was noted.

The patient continued in a moribund state and on the following day was subjected to exploratory laparotomy, via a right paramedian incision; it revealed much blood-stained purulent material above and below the liver; in the right thoracic and lumbar paravertebral gutter; and the right retroperitoneal space. The appendix was not indentified; however, extensive exploration was deferred in view of the patient's poor condition. Gastrostomy was performed, many drains were placed in the abdomen, and the patient was given five units of whole blood. The flank incision was extended and repacked.

Postoperatively, the BUN rose to 68 mg per 100 ml, and the urinary output fell to less than 10 cc per hour, despite an additional three units of blood. Hematocrit at this time was 36 percent. Intravenous Isuprel® was required to maintain systolic blood pressure at 80 mm Hg, and anuria continued to the time of death early on the 12th hospital day.

Necropsy

At postmortem examination, the body was that of a well-developed, poorly nourished, elderly man, showing recent surgical interventions on the abdomen, the flank, the scrotum, the chest, and the trachea.



FIG. 1. Terminal ileum (I); cecum (C); and residual, proximal portion of appendix (arrow) (photographed after evisceration).

In the abdominal cavity, a shaggy, gray, hemorrhagic exudate filled the right lower quadrant, with many soft, necrotic adhesions between loops of terminal ileum, and a large collection of gray fibrinous exudate in the right subphrenic space. The anterior wall of the gastric antrum was sutured to the overlying abdominal wall as a patent, intact gastrostomy; multiple drains were placed into the right subphrenic space, subhepatic space, and right lower quadrant. The right retroperitoneal space was full and irregularly fluctuant.

The terminal ileum, cecum, and ascending colon were incised in situ. The proximal appendiceal mucosa was moderately injected. The appendiceal lumen was directed posteriorly and the distal portion of the appendix was absent (Fig. 1). It ended sharply in a large, irregular, poorly defined retroappendiceal and retroperitoneal abscess cavity, which was well organized at its periphery. This abscess extended up the right paravertebral gutter, and communicated with a large, organizing subphrenic abscess. The right leaf of the diaphragm was greatly thickened and had an irregular, shaggy perforation (Fig. 2). The abdominal surface of the diaphragm was covered by an organizing hematoma in addition to fibrinous and fibrous exudate. The thoracic aspect of the diaphragm was adherent to the base of the right lung.

The thoracic drain was in place and the right thoracic cavity contained approximately 100 cc of hemorrhagic, purulent fluid. The right lung weighed 1,050 grams, and its pleural surface was covered by a fibrinous exudate. The entire lung was congested and consolidated, and had a large, irregular, 7.0 cm-sized abscess cavity in the right lower lobe (Fig. 3). The cavity contained about 200 cc of viscid, gray, necrotic material. The remainder of the right, and the entire left lung was diffusely consolidated, and, microscopically, showed acute and organizing bronchopneumonia.

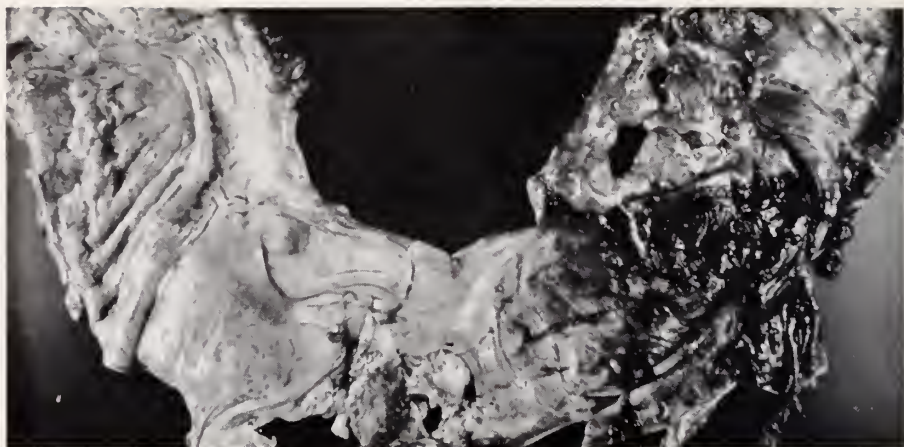


FIG. 2. Thoracic aspect of diaphragm, showing irregular, necrotic perforation of right leaf.



FIG. 3. Right lung, showing irregular abscess cavity in lower lobe (arrows).

The right internal inguinal ring was widely patent and communicated directly with the right scrotum. The right testis and spermatic cord were absent and the serotal sac was thickened by organizing exudate and edema.

The dome of the right lobe of the liver was covered by organizing exudate and there was a soft capsular hematoma at the inferior aspect of the right lobe, lateral to the gall bladder. The gall bladder, itself, contained 10 small, smooth, multifaceted black stones.

The remainder of the necropsy examination did not reveal pertinent abnormal findings, except for the nervous system, where a subdural hematoma, showing early organization, covered the frontal and parietal lobes.

Discussion

The essentially nonexistent mortality and morbidity of acute appendicitis no longer holds true once perforation occurs (2). The usual immediate complications of perforated appendicitis are peritonitis and intra-abdominal abscesses. Intra-abdominal abscess formation may be limited to the area of the appendix itself; may be situated more distantly in the subphrenic space or the pelvis; or may be located in other organs, most frequently the liver. If surgery is performed, the skin and subcutaneous tissue of the incision may develop suppuration. Extra-abdominal abscess formation is a most unusual occurrence in the natural history of acute, perforative appendicitis.

Direct extension into the thorax, from an infective process arising in the appendix, was detailed in 1886 by Reginald Fitz (3). He noted that "the extension of a secondary paratyphlitis may cause perforation of the diaphragm with a consecutive pleurisy or pericarditis." The pulmonary and pleural involvement following appendicitis was discussed extensively, in 1905, by Kelly and Hurdon (4a). They described the frequent occurrence of pulmonary congestion, pulmonary edema, and bronchopneumonia, as well as lobar pneumonia, associated with acute appendicitis. They noted gradations from a very slight fibrinous pleuritis in almost all the cases of pneumonia, to the extensive pyothorax found in four cases. Their experience indicated that the most frequent pulmonary complication was pleuritis, although they pointed out that the incidence of this was much less than the 38 percent they quoted from the report of Wollbrecht (4b). They further warned that "in several instances it has happened that a pleural empyema has been discovered and operated upon, while the primary cause, a suppurating appendix, has not been discovered until the postmortem. It behooves the operator, therefore, in every case of empyema, particularly in right-sided affections, and above all when the pus is ill-smelling, to bear in mind this possibility, and to make such examinations of the right iliac fossa (rectal above all!) as shall decide the question" (4c). Deaver also mentioned the occurrence of purulent pleurisy or empyema as the result of extension of a subdiaphragmatic abscess, with accompanying pulmonary abscess, that may, or may not be expectorated externally (5a).

Pleurisy was the most frequent complication of subphrenic abscess in Ochsner and DeBakey's series (6). They indicated that perforation of

the diaphragm by a subphrenic abscess will result in either empyema or pneumonitis with bronchial fistula, depending upon whether or not a free pleural space exists. If the pleural surfaces are adherent, rupture into the lung ensues, with the development of a basilar pneumonitis and bronchial fistula.

Extension of a perforated appendix to the flank was described by Krogius, in 1901. His report, quoted by Kelly and Hurdon, concerned the case of a 48-year-old man "who had an enormous abscess associated with a perforated appendix, pointing in the gluteal region. This was at first mistaken for a hernia; but operation showed a large pus cavity over the trochanter major, and the muscles in the gluteal region were full of pus" (4d).

Deaver described many cases with unusual phlegmonous spread from retroperitoneal abscesses secondary to ruptured appendicitis (5b). He indicated that the suppurative process may follow the course of the iliac vessels; may present behind Poupart's ligament; may involve the perirenal space and the subphrenic space, as well as perforate through the diaphragm; and quoted Sonnenburg's case of a serotal pyoceles, resulting from "infection of a patulous vaginal tunic of the testicle" (5c).

Discussions of the complications of acute appendicitis have become unusual in contemporary medical literature, and cases resembling either that, or Krogius or Sonnenburg are most unusual. Further, we are unable to find any one case having the three unusual complications presently reported.

It is not difficult to explain the anatomical routes of spread of suppuration in the formation of the extra-abdominal abscesses here described. The pulmonary abscess is clearly secondary to perforation of the diaphragm by suppuration in the right subphrenic space. Extension of sepsis, via the subphrenic lymphatics, may have been a contributing factor, but this cannot be proved in the face of the extensive necrosis in the subphrenic area. It is reasonable to assume that the patient's inguinal defect provided a route of minimal resistance to both the right flank and the right serotal sac.

In order, however, to explain the basis of the extensive spread of suppuration, it is necessary to briefly consider the problem of acute appendicitis in the aged.

The classic textbook descriptions of acute appendicitis do not apply, in a significantly large group, to elderly patients. Acute appendicitis in the aged patient is likely to have reached the stage of perforation before symptoms and signs permit accurate diagnosis (1). This situation has been attributed to several factors: the threshold to pain in the aged generally is increased, partly from tolerance by habit and partly from some loss of cerebral sensory interpretation (2); the febrile response may develop more slowly, or not at all (7); and the leukocyte count is often only slightly elevated, and may rise at a surprisingly slow rate (8). The subtlety of symptoms and the more virulent pathologic course of acute appendicitis in the elderly, permits the disease process to progress rapidly and insidiously, contributing to a mortality rate 16 times greater in this age group than in the younger patient (9).

Chills, a symptom in the present case, appear to be of ominous import in the aged, and may signify the presence of a peritoneal complication (1).

The etiology of acute appendicitis is the same in the aged as in other age groups; however, the structure of the organ may contribute to perforation in the older patient (10). Most of the lymphoid tissue of the appendix has disappeared, and fibrous atrophic changes have occurred. There may be concomitant vascular alterations, which result in impaired circulation and an inability to respond to the demands of inflammation for increased blood supply. When the devitalized appendix is subjected to obstruction and suppuration, perforation may readily occur.

Wolff and Hindman found gross perforation in 58 percent of 88 patients in the over 60 age group, or more than twice as frequently as in the 30 to 40 year group (1). Covan and Wheeler studied 28 patients with acute appendicitis, all more than 60 years old (7). They found evidence of perforation in 17 of 21 patients operated upon more than 24 hours after onset of symptoms, but in only 1 of 6 patients operated on before that time. Perforation, in their series, was also the chief cause of mortality.

The difficulties in diagnosing acute appendicitis in the aged patient are both clinically and statistically significant. Serious errors or delays in diagnosis occur more than four times as often in the elderly patient than in younger adults (1). These problems are compounded by the fact that the disease process is frequently more fulminant in the aged; yet, early diagnosis is the important key in reducing the mortality and morbidity.

Summary

A 68-year-old man entered the hospital complaining of chest pain and was found to have a right pleural effusion. Abscesses of the right flank and right scrotum developed which did not respond well to medical or surgical attempts at therapy. Physical signs localizing to the abdomen were minimal, and a large right lung abscess developed, with the patient's course rapidly progressing to death. At necropsy, a perforated, inflamed appendix was found, causing a large, irregular suppuration in the right retroperitoneal and right subphrenic spaces, with perforation through the right hemidiaphragm to produce a large right lower lobe pulmonary abscess. The problem of acute appendicitis in the aged is discussed.

References

1. Wolff, W. I., and Hindman, R.: Acute Appendicitis in the Aged, *Surg Gynee Obstet* 94:239-247, 1952.
2. Allen, J. G.: Appendicitis and the Acute Abdomen, *Surgery Principles and Practices*, 2nd ed, Harkins, H. N., Moyer, C. A., Rhoads, J. E., and Allen, J. G., eds., J. B. Lippincott, Philadelphia 1961, pp 846-874.
3. Fitz, R. H.: Perforating Inflammation of the Vermiform Appendix; with Special Reference to its Early Diagnosis and Treatment, *Tr A Am Physicians* 1:107-144, 1886.

4. Kelley, H. A., and Hurdon, E.: *The Vermiform Appendix and its Diseases*, W. B. Saunders and Company, Philadelphia 1905 (a) p 247, (b) p 402, (c) p 459, (d) p 205.
5. Deaver, J. B.: *Appendicitis*, 4th ed., P. Blakiston, Philadelphia 1913 (a) p 343, (b) p 137, (c) p 139.
6. Ochsner, A., and DeBakey, M.: Subphrenic Abscess, *Surg Gynec Obstet* 66:426-38, 1938.
7. Covan, A. G., and Wheeler, H. B.: Early Perforation in Appendicitis After Age 60, *JAMA* 197:745-48, 1966.
8. Hubbell, D. S., Barton, W. K., and Solomon, D. D.: Leukocytosis in Appendicitis in Older Persons, *JAMA* 175:139-141, 1961.
9. Williams, J. S., and Hale, H. W., Jr.: Acute Appendicitis in the Elderly, *Ann Surg* 162:208-12, 1965.
10. Simpson, D. G.: Acute Appendicitis in the Aged, *Brit Med J* 2:986-7, 1946.

Received for publication November 19, 1968

Neurologic Syndromes Associated with Primary Thrombocythemia*

GARY KORENMAN, M.D.

Primary hemorrhagic thrombocythemia (PHT) is a rare hematologic disorder considered by most hematologists (1, 2) to be part of the spectrum of myeloproliferative diseases. The following general criteria are required for diagnosis: 1) a history of thrombohemorrhagic occurrences; 2) peripheral platelet count persistently above 800,000/mm³; 3) hyperplastic bone marrow with predominance of megakaryocytes and platelet masses; 4) peripheral erythrocyte count less than 6,000,000/mm³, hemoglobin and hematocrit less than 18 gm% and 54 ml%, respectively; 5) white blood count less than 50,000/mm³, and absence of leukemic infiltration by biopsy, or at necropsy. Ancillary findings include palpable spleen; eosinophilia and basophilia in the peripheral smear. While thrombocytosis is well known to occur transiently postpartum, with infections and malignancies, and postsplenectomy, it is found after months and years in PHT. While persistent thrombocythemia may be found in polycythemia vera or chronic myelogenous leukemia, the presence of these disorders excludes the possibility of considering a patient to have PHT.

Current medical literature is replete with hematologic studies of PHT. Gastrointestinal hemorrhage is cited as the most common manifestation of the disorder. The purpose of this report is to review the experience at The Mount Sinai Hospital with neurologic manifestations and complications of PHT, and to emphasize the frequent associations of PHT with neurologic dysfunction.

Seven patients were found (1964-1968) who satisfied the above criteria for PHT. Five of these patients had associated neurologic dysfunction, and in four patients the neurologic illness prompted admission to the hospital and led to the diagnosis of PHT.

Case Reports

Case 1. J.C., (MSH #236 714), was a 40-year-old woman at the time of her first hospital admission in December 1963. At that time she gave a history of anemia for 5 years, pain and cyanosis of the hands and feet in cold weather for 1½-2 years, and hypertension with systolic readings up to 250 mm Hg for 2 years. Two weeks prior to admission she had an episode of syncope while in a subway station. Subsequently, she noticed tingling in both feet and hands, and extreme weakness of the right arm and hand. Physical examination was normal except for hepatosplenomegaly. Blood pressure was normal. She was anemic with a hemoglobin of 7.5 gm%. Workup for anemia including bone marrow was unrevealing. Platelet count at that time was 224,000. WBC alkaline phosphatase was elevated to 143 units. It was thought she had a myeloproliferative disorder with iron deficiency anemia. She was treated with oral iron and responded well. As the anemia was

*This work was supported by Training Grant #NB 05072 from the Department of Neurology, The Mount Sinai Hospital, New York, N.Y.

corrected, the platelet count was noted to rise to levels of 1.5 million. She was then treated with Myleran® 2 mg daily, and did well until July 1967 when she was readmitted because of tarry stools, dizziness, and a history of several hours of difficulty in speaking, with drawing up of the right side of the face. General physical examination was unremarkable. Upon neurologic examination, the patient was dysarthric, and there was fine horizontal nystagmus on right lateral gaze. On left lateral gaze, there was nystagmus with a clockwise rotatory component. Sensation to pin prick was markedly impaired on the right side of the face in the distribution of the first and second divisions of the trigeminal nerve. The right corneal reflex was slightly diminished, and there was mild ptosis on the right. There was right facial weakness that did not include the frontalis muscles, and there was decreased power of protrusion of the tongue toward the right. Rapid alternating movements of the tongue were impaired. Power was normal bilaterally in the extremities. Heel to knee to shin test was performed slowly on the right. Pin prick sensation was decreased from the neck down on the left side. Examination one week later revealed clearing of the above findings, and the patient was aphasic with a right homonymous hemianopsia; right hemiparesis; right extensor plantar response; impaired optokinetic nystagmus, with the tape moving from patient's right to left, and normal from left to right. There was impairment of position sense in the right hand and foot, poor stereognosis and 2 point discrimination of the right hand and fingers, respectively. Skull series, brain scan, and lumbar punctures on two occasions were completely normal. EEG on July 24 showed 2-6 cps of activity up to 80 uv at the left frontotemporal derivations. A repeat EEG on August 7 showed 1.5-3 cps of activity up to 150 uv diffusely on the left with some accentuation at the frontotemporal area. In addition there was bilateral 4-7 cps of activity up to 90 uv with asymmetry (left more than right). This was interpreted as being more severely abnormal than the first EEG. Her hematologic work-up included normal bleeding, clotting times, normal clot retraction, and partial thromboplastin test. Fibrinogen was 330 mg%, and prothrombin time was 17 seconds with control, 16 seconds. Platelet counts with the patient taking Myleran® were consistently under 750,000 on numerous occasions, and at discharge the platelet count was 300,000 with hemoglobin 11.7 gm%. She improved gradually during a two-month period and was discharged to go home. The patient was well until January 24, 1968, when she had a generalized convulsion and awakened with a right hemiparesis, and was unable to communicate. She was admitted on January 31, after being treated at another hospital. On examination she was aphasic, with inability to express herself and anomia as the major components. She comprehended and followed complex commands in normal fashion. In addition she was dysarthric, experiencing poor alternating movements of the tongue. There was a right hemiparesis with the arm weaker than the leg. There was coarse horizontal nystagmus on right and left lateral gazes, and fine nystagmus on upward gaze. Tape optokinetic nystagmus was absent to the left, right, up, and down. A right homonymous hemianopsia was apparent to double simultaneous finger motion, and was present in the right lower quadrant to single stimulation. There were no abnormalities of the deep tendon reflexes. There was a hemihypesthesia of double simultaneous touch and pin prick over the right arm, leg, and trunk. An EEG showed long runs of 1-3 cps of activity up to 150 uv diffusely and bilaterally, alternating with 5-7 cps of activity up to 40 uv bilaterally. There was no apparent change in the level of consciousness during these alternations. Hematologic laboratory data was normal except for prothrombin time of 15 seconds with a control of 12 seconds. The patient improved slowly and was left with a mild right hemimotor and hemisensory syndrome at discharge in mid-February 1968.

Case 2. L.G., (MSH #258 711), was a 69-year-old man admitted to the hospital in June 1966 because of severe pain in the soles of both feet and his right calf for two weeks. His past medical history included rheumatic heart disease with mitral insufficiency, aortic insufficiency and stenosis, and protracted congestive heart failure with several episodes of pulmonary edema during the previous six years. In addition he had mild diabetes mellitus.

On physical examination he appeared acutely and chronically ill with dyspnea, cyanosis, and telangiectasis over his face. There was marked cardiomegaly with a grade IV apical systolic ejection murmur radiating to the left axilla; a grade III blowing aortic systolic murmur; and a grade IV blowing diastolic murmur in the aortic area. The liver was palpable with a positive hepatojugular reflux. There was marked tenderness of the left and right calf areas. There was no splenomegaly, and no evidence for thrombophlebitis. On neurological examination the positive findings were decreased vibration sense in both lower extremities, absent ankle jerks, and tenderness of the calf muscles. A lumbar puncture was performed and was clear and colorless under normal pressure with normal protein, glucose, and no cells. A muscle biopsy of the right quadriceps and right gastrocnemius showed small group atrophy, a pattern suggestive of neurogenic origin. Laboratory data of significance were as follows: urinalysis with 2+ protein, 2-3 hyaline casts, 3-5 WBC, and 1-2 fine granular casts; EKG compatible with previous anteroapical myocardial infarction; hemoglobin 12.2 gm%, hematocrit 40 ml%, 4.2 million RBC, WBC 17,200 with normal differential, and platelet count 1,178,000. Repeat platelet count was 1,264,000. Prothrombin time was 17 seconds with control of 12 seconds. Bone marrow aspiration revealed increased megakaryocytic activity in an otherwise normal marrow. The patient was treated for his severe radiculomyelopathy with intrathecal methylprednisolone, 40 mg every three days, with progressive improvement of his walking, and he was discharged August 1 to a convalescent home. He was readmitted to the hospital August 4, 1966 because of onset of agitation, disorientation, and aggressive and abusive behavior. On examination, he did not know the date, name of the President of the U.S.A., and was unable to perform simple calculations. Laboratory data was unrevealing except for platelet count of 1,200,000. He was discharged with normal mental status examination on August 27, only to be readmitted September 2, with recurrence of his organic mental syndrome. EEG was markedly abnormal with 2-5 cps of activity up to 90 uv seen diffusely and bilaterally. This was compared to an EEG obtained July 6, 1966 which showed 5-7 cps of activity diffusely bilateral, with infrequent burst of 2.5-4 cps of activity up to 100 uv. It was felt that the present EEG was more severely abnormal. He was treated with chlorpromazine and oral prednisone. Repeat hematologic workup, including bone marrow biopsy, was unrevealing except for platelet counts varying from 900,000 to 1,380,000 on six occasions. The patient was discharged October 1 and did relatively well until April 30, 1967 when he was readmitted because of sudden onset of stupor. Although the stupor cleared within 48 hours, the patient had evidence of a severe organic mental syndrome which persisted for 5-6 weeks. He was treated with Myleran® 6 mg daily starting June 5, with progressive normalization of the peripheral platelet count. He had a similar episode of progressive, rapid onset stupor in January 1968, and this cleared slowly over a period of several weeks. At no time was there evidence of focal neurological findings. He was discharged to a convalescent nursing home where he is currently being followed.

Case 3. H.B., (MSH #426 958), was a 56-year-old man admitted to the Elmhurst Hospital division of The Mount Sinai Hospital on August 19, 1967 with a history of being found on the floor of his apartment on the day of admission. He was unable to walk because of weakness in the left lower extremity. In 1960 the patient had an episode of left hemiparesis from which he recovered, and was able to ambulate with some dragging of the left leg. On past admission he was found to be diabetic and was given tolbutamide for control. Physical examination at this admission revealed the patient to be confused and disoriented, but these findings cleared within 24 hours. There was a spastic left hemiparesis with increased deep tendon reflexes and positive Hoffman on the left, and bilateral extensor plantar responses. There were no other neurological findings and the general physical examination was normal. Subsequently the patient was observed to have two episodes of twitching of the left arm, each lasting ten seconds. He was incontinent of urine with these paroxysms, but there was no loss of consciousness. Lumbar puncture revealed clear and colorless fluid with normal pressure, protein 52 mg%, glucose 110 mg%,

with a simultaneous blood sugar 184 mg%. EEG revealed a moderate amount of 4-6 cps of activity up to 30 uv at the right temporal derivations. Skull and chest x-rays were normal. Blood chemistries were all normal except for elevated blood sugar to 220 mg%. Admission hemoglobin was 13.6 gm%; WBC 8,800; hematocrit 42 ml%. Differential white blood count was normal. Platelet counts varied from 980,000 to 1,086,000 during a period of ten weeks. There was no further follow-up.

Case 4. L.J., (MSH #065 473), was an 81-year-old man admitted to the hospital October 30, 1967 with a history of a fall in early September 1967. This required scalp sutures. At that time he was taking anticoagulant medication for thrombophlebitis. He had several falls in the three weeks preceding admission, and for one week prior to admission he had become increasingly apathetic and drowsy. In addition, he had difficulty in expressing himself. On the day prior to admission he was able to walk with support, but he tended to veer toward the right. On examination, the vital signs were normal. There was a grade $\frac{1}{6}$ systolic murmur, fine rales at both lung bases, a 2-3 finger-breadth liver palpable, and flat neck veins were visible. Upon neurologic examination spontaneous speech was normal, and there was no anomia. He spelled "cat," but reversed it as "cant." He was able to spell "hand," but could not attempt to reverse it. He was not able to name the President, nor did he recognize people who were familiar to him. He was oriented to time, place, and person. There was a right homonymous hemianopsia to double simultaneous finger motion. The pupils were small and reactive. Fundi could not be visualized. There was drift of the right upper extremity with mild paresis. Deep tendon reflexes were active and symmetrical, and there were bilateral extensor plantar responses. With double simultaneous stimulation using pins, he extinguished the right arm and right leg. There were position sense errors in the right lower extremity and both hands. Vibration was diminished below the iliac crests bilaterally. Laboratory data showed a hemoglobin 12 gm%; WBC 7,100 with normal differential count; and increased platelets on smear. Prothrombin time was 20 seconds, with control 13.5 seconds. Sonoencephalogram showed a 2 mm shift from left to right. Lumbar puncture was under 100 mm CSF pressure, clear and colorless; with protein 99 mg%, and no cells. Skull series showed the pineal to be shifted 5 mm to the right. Chest x-rays showed recent fractures of the right IXth and Xth ribs, and a calcified granuloma in the left upper lobe. Peripheral platelet count was 1,700,000 and 2,044,000. Bone marrow was hypercellular with marked increase in megakaryocytes. EEG on admission revealed 1.5-3 and 4-6 cps of activity diffusely on the left, with decreased amplitude, and frequency of the alpha activity on the left. There was also beta asymmetry with decreased amplitude and amount on the left. Repeat EEG two weeks later was unchanged. Brain scan with $\text{Te}^{99\text{m}}$ showed a left posterior-frontal to parietal lesion. A repeat brain scan 2½ weeks later showed the lesion to be smaller and less well defined. Right brachial arteriography with compression of the left carotid artery showed the anterior cerebral artery to be shifted from left to right; depression of the Sylvian point on the left with medial displacement; and shift of the internal cerebral vein from left to right. The patient improved slowly and was discharged on Myleran,[®] on November 29, 1967. A follow-up platelet count in mid-December 1967 was 900,000.

Case 5. A.H., (MSH #256 353), was a 76-year-old man at the time of his admission in August 1964. There was a ten week history of daily, intermittent, right facial pain. The pain was paranasal and precipitated by drinking, chewing, or palpation of the right side of the nose. There was no history of vertigo, headache, incoordination, or visual complaints. In addition, there was a two month history of 10 lb weight loss, anorexia, and tarry stools. The patient was a known diabetic since 1954 and required tolbutamide 500 mg daily since 1959 for control. Upon physical examination there was a palpable spleen three finger-breadths below the left costal margin. There was a question of decreased pin prick sensation in the area of facial pain, but no other neurological findings. The splenomegaly had also been found on examination in July 1962, at the Strang

Clinic in NYC. His admission laboratory data revealed a hemoglobin of 10.8 gm%, erythrocyte count 3.5 million/mm³, white blood count 10,050, and hematocrit 32.5 ml%. Differential white count was normal. Platelets were 996,000/mm³. Sternal bone marrow was slightly hypercellular with increased granulocytic activity. Megakaryocytes were markedly increased and very active. Repeat platelet count was 776,000. A GI series, barium enema, skull and chest x-rays were normal. EKG and EEG were normal. Brain scan with RIHSA was normal. The patient was discharged and lost to follow-up.

Discussion

Of the thrombohemorrhagic complications of primary hemorrhagic thrombocythemia, neurologic disturbances have seldom been commented upon by other examiners, despite the apparent frequency of nervous system involvement.

Ozer et al (4), in reporting seven cases of PHT, had three patients with neurologic difficulty. Their case four had uncinat and Jacksonian seizures, and the authors remark upon a ten month hematologic remission concordant with a decrease in seizure frequency. Case six had paroxysms of dizziness, dysarthria, and right hemiparesis. There is no further information about this patient's neurologic status or course. Case seven was referred to the hospital for evaluation of mental status. A right hemiparesis developed and the patient had a Jacksonian seizure. The patient improved and was ambulatory when the hemiparesis recurred. Shortly thereafter, she lapsed into coma and died. At autopsy, there was a massive intracerebral hemorrhage. Shaw and Oliver (1) presented three patients with PHT. One was a 32-year-old man with a right hemiplegia. He subsequently developed a seizure disorder. Another of their patients was said to have Parkinson's disease, but this is not further detailed. Jasinski (5) reported a 68-year-old woman with herpes zoster frontalis (right side) who developed a left hemiparesis one month later. There was splenomegaly, and the platelet count was 1,780,000. There was no evidence of leukemia. Schupfbach and Herrmann (6) reported a 45-year-old man with hepatosplenomegaly and a platelet count of 1,650,000. Bone marrow gave evidence of increased numbers of megakaryocytes. This patient developed a spastic right hemiparesis and aphasia. Carotid arteriography demonstrated an occlusion of the left middle cerebral artery. Olivarius (7) reported a 58-year-old man with amaurosis fugax, a pulseless left carotid artery, and paroxysms of right hemianesthesia and hemiparesis. The platelet count varied between 1,332,000 and 2,360,000. Bone marrow gave evidence only of increased numbers of megakaryocytes. The remainder of the hematologic evaluation was normal. Six weeks after discharge, the patient returned and was found to be anemic. Workup revealed stem-cell leukemia. It is apparent from this case that long term follow-up is essential in patients presumed to have PHT. This has been succinctly pointed out by McCabe et al (3), who reviewed all the published cases of PHT up to 1955, and presented a patient who developed myeloblastic leukemia after three years' follow-up.

In our patients, follow-up is less than 1 year in three patients, and 3-4 years in two patients. Of interest, the two patients followed for the longest period present the most diverse and perplexing neurologic disturbances. One (case 1), was observed to fluctuate from a picture of dorsolateral medullary dysfunction to left cerebral difficulty, back to bilateral brainstem dysfunction plus left cerebral encephalopathy after a convulsion. The second patient (case 2), presented with evidence of a radiculomyelopathy, and later an organic mental syndrome with marked swings in the level of consciousness. At first the organic mental syndrome seemed to change independently of the level of consciousness. In addition, there was no apparent relationship to degree of platelet elevation. In case 3, the patient had a left hemiparesis in 1960 and recurrence of the same difficulty in 1967. The question must be posed if we are dealing with arteriosclerotic cerebrovascular disease in a patient with diabetes mellitus, and if the neurologic involvement is unrelated to PHT. With present information, the question cannot be answered. In case 4, the patient was taking anticoagulants and sustained a mild head trauma. While this was probably sufficient for development of a subdural hematoma, did the thrombocythemia with endogenously prolonged prothrombin time contribute? It is well known that patients with PHT tend to have

TABLE I

Case	Previous thrombo-hemorrhagic Sx	Neurologic symptoms	Platelets	HGB, WBC, RBC	Bone marrow	Cerebro-spinal fluid	Electro-encephalogram
1 (J.C.)	Raynaud's Sx? Duodenal Uleer	Left dorsolateral medullary syndrome, and left cerebral dysfunction. Both of these symptoms fluctuated.	224,000 to 1,574,000	Hg—7.5 gm WBC—9400 Het—25 RBC—4.09 Prothrombin time 16/12	Erythroid Hyperplasia	Normal	Abnormal in left fronto-temporal area.
2 (L.G.)	none	Radiculomyelopathy, and then organic mental syndrome with marked fluctuations in levels of consciousness.	1,178,000 to 1,264,000 (1st adm)	Hg—12.2 WBC—17,200 RBC—4.2 Protine—17/12 sec	Hypercellular with increased megakaryocytes	Normal	Bilaterally abnormal on repeated exams.
3 (H.B.)	Left hemiparesis in 1960 from which he recovered	Left hemiparesis with focal seizures and confusion.	980,000 to 1,112,000	Hg—13.6 WBC—8,800 Het—42%	Slightly increased megakaryocytes	Normal	Abnormal in right temporal derivations.
4 (L.J.)	Thrombophlebitis (on anticoagulant)	Mild head trauma, followed by confusion, right hemiparesis and right homonymous hemianopsia.	1,700,000 to 2,044,000	Hg—10.6 WBC—5,800	Hypercellular with marked increase in megakaryocytes	Protein —99 mg	Severe left cerebral dysfunction. This was unchanged on repeat exams.
5 (A.H.)	Two month history of tarry stools	Ten weeks of right faecal pain. ?Decreased pin sensation on face.	996,000	Hg—10.6 RBC—3.5 WBC—10,050	Increase in myeloid and megakaryocytes	Not done	Normal.

prothrombin times in the 50 percent range. The addition of exogenous anticoagulants to a patient with an already prolonged prothrombin time may have been sufficient reason, with minor head trauma, to result in the neurologic difficulty. We cannot definitely relate trigeminal neuralgia in case 5 to his thrombocythemia, as the follow-up is too brief. In regard to treatment, our patients responded hematologically to immunosuppressive therapy (Busulfan). However, we were unable to correlate hematologic remission, in any of our patients, with neurologic remission. Levine and Swanson (8) reported one patient with transient ischemic episodes of PHT, who became symptom free for five months during normalization of the platelet count. A positive correlation is difficult to conclude, as many patients with transient ischemic episodes are symptom free for long periods (Table I).

Summary

We have presented five cases of primary hemorrhagic thrombocythemia with neurologic complications, examined at The Mount Sinai Hospital since 1964. These were culled from a total of seven patients with PHT during the same time period (1964-1968). The neurologic manifestations were varied, involving cerebrum diffusely or focally, brainstem, spinal cord, and roots. Four of five patients presented a neurologic disturbance as the prime factor in admission to the hospital. There was no apparent relationship between immunosuppressive therapy and neurologic improvement. Awareness of primary thrombocythemia has been emphasized as a diagnostic possibility in patients with neurologic dysfunction.

Acknowledgment

The author wishes to express his gratitude for the encouragement of Dr. Morris B. Bender in the preparation of this paper.

References

1. Shaw, S., and Oliver, R. A. M.: Primary Hemorrhagic Thrombocythemia, *Proc Roy Soc Med* 51:768, 1958.
2. Levin, W. C., Cefander, D. R., and Guest, M.: The Mechanism of Hemorrhagic Manifestations Associated with Thrombocythemia, *J Lab Clin Med* 46:930, 1955.
3. McCabe, W. R., Bird, R. M., and McLaughlin, R. A.: Is Primary Hemorrhagic Thrombocythemia a Clinical Myth? *Ann Intern Med* 43:182, 1955.
4. Ozer, F. L., Truax, W. E., Miesch, D. C., and Levin, W. C.: Primary Hemorrhagic Thrombocythemia, *Amer J Med* 28:807, 1960.
5. Jasinski, B.: Zur Pathogenese der Thrombocythämie, *Acta Haemat* 2:145, 1949.
6. Schupf Bach, A., and Hermann, E.: Thrombosekrankheit bei essentieller Thrombocythämie, *Schweiz Med Wschr* 84: 95, 1954.
7. Olivarius, B. S.: Cerebral Manifestations in Thrombocythemia, *Acta Psychiat et neurol Scandinav* 32:77, 1957.
8. Levine, J., and Swanson, P. D.: Idiopathic Thrombocytosis: A Treatable Cause of Transient Ischemic Attacks, *Neurology* 18:711, 1968.
9. Kissel, P., et al: Wallenberg's Syndrome during Chronic Thrombocythemia in a Splenectomized Patient, *Ann Med Nancy* 3:1004, 1964.

Received for publication October 7, 1968

RADIOLOGICAL NOTES

Ischemic Colitis: Presentation of Seven Cases

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., Co-Editors

The following seven cases will be presented in an attempt to illustrate and elucidate the entity of ischemic colitis, otherwise known as segmental vascular colitis, or colonic infarction (1). This disease is being encountered by radiologists with increasing frequency, and it is of more than academic importance to render the proper diagnosis. During the acute stage, the radiologist can almost unequivocally tell the clinician that the patient is suffering from a self-limiting disease requiring only conservative therapy, and not from a chronic process, such as ulcerative colitis or a colonic neoplasm.

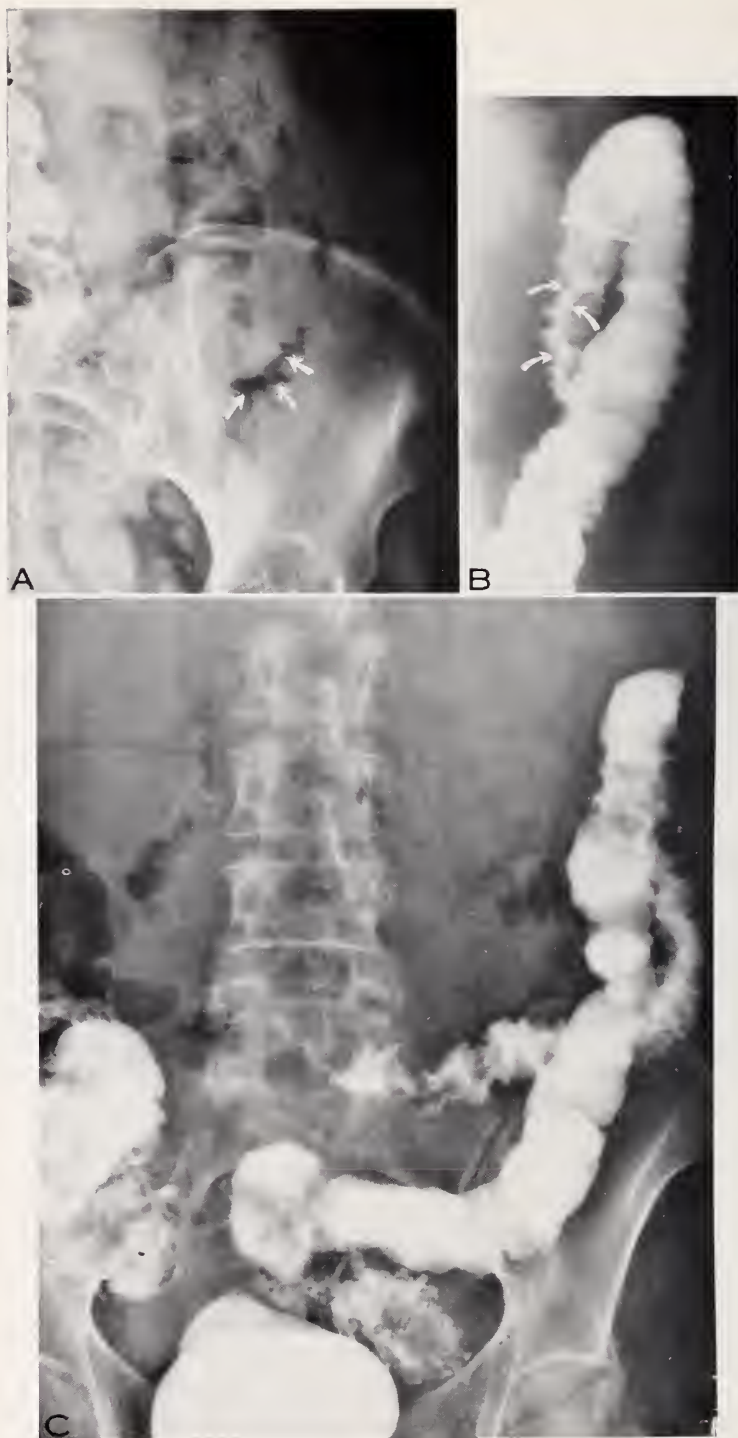
CASE NO. 325

A 60-year-old woman was seen because of the acute onset of abdominal pain and bright red bleeding. Sigmoidoscopy was negative, but blood was seen coming from above. The vital signs were normal. Preliminary radiograph of the abdomen revealed a collection of gas outlining the mid-descending colon. The affected segment appeared narrowed with thickening of the folds (Fig. 2A). Emergency barium enema confirmed the presence of a narrowed segment of the left side of the colon near the splenic flexure (Figs. 2B and 2C). The folds were thickened with thumb-print defects along the walls of the narrowed segment.

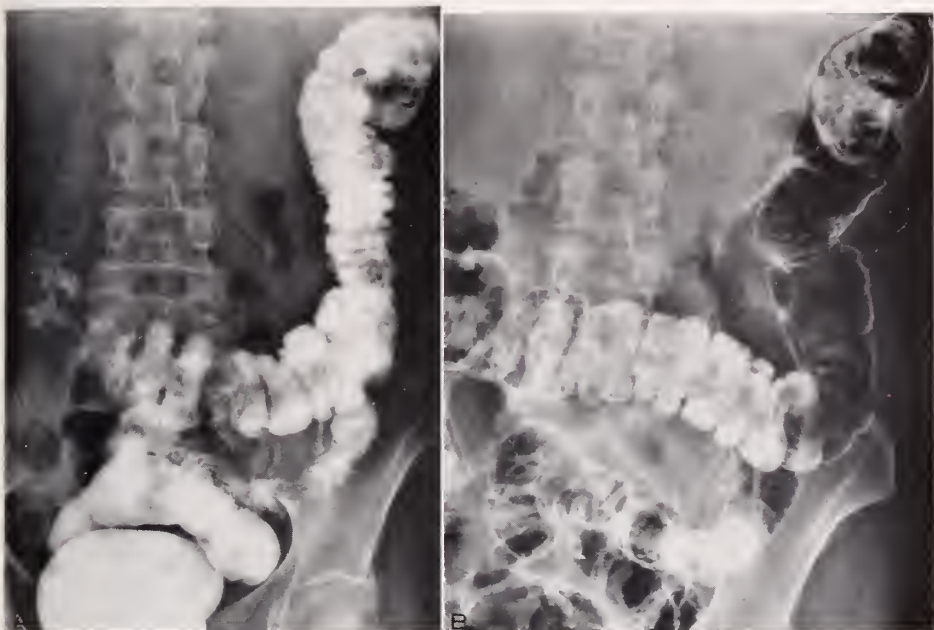
The patient was treated with conservative measures, and repeated examination three weeks later revealed return to an entirely normal colon (Figs. 3A and 3B). Clinically, the patient made an uneventful recovery. The colon was similar in appearance to that seen five years before the present illness (Fig. 1).



Case 325, Fig. 1. Barium enema performed five years before the present illness reveals normal distensibility of the entire colon.



Case 325, Figs. 2A-C.



Case 325, Fig. 3A. Repeat barium enema three weeks after Fig. 2, reveals a return of normal distensibility, fold pattern, and caliber of the affected segment.

Case 325, Fig. 3B. Air contrast studies confirm the presence of normally distensible walls.

Case 325, Fig. 2A. Preliminary film of the abdomen reveals a collection of gas outlining the mid-descending colon. This shows a narrowed segment of colon with thickened folds indenting the air column (arrows).

Case 325, Fig. 2B. During the course of a barium enema, spot film shows thickened folds, irritability, slight narrowing, and marked distortion of the fold pattern, corresponding to the findings described on the preliminary film of the abdomen (arrows). There is no evidence of discrete ulcerations.

Case 325, Fig. 2C. The extent of the lesion appears to correspond to the distal transverse and proximal descending colon.

CASE NO. 326

A 65-year-old patient was admitted to the hospital with a clinical history of a sudden onset of severe abdominal pain, nausea, diarrhea, and slight elevation of temperature. There was some bright rectal bleeding. The vital signs were normal, as was the examination of the abdomen. An emergency barium enema revealed a long segment of narrowing, and irritability involving the distal transverse and proximal descending colon. This segment was anastomotic and concentrically narrowed, with thickening of the folds and distortion of their pattern (Figs. 1A, 1B and 1C). The patient was treated with antibiotics and other conservative measures, and was discharged well, two weeks after the initial episode. A follow-up examination performed three months later revealed some shortening of the splenic flexure, with irregular flattening along the medial wall of the distal transverse and proximal descending colon (Figs. 2A, 2B, and 2C). This area was narrowed and lacked normal haustration. The remainder of the large intestines was normal in every respect.

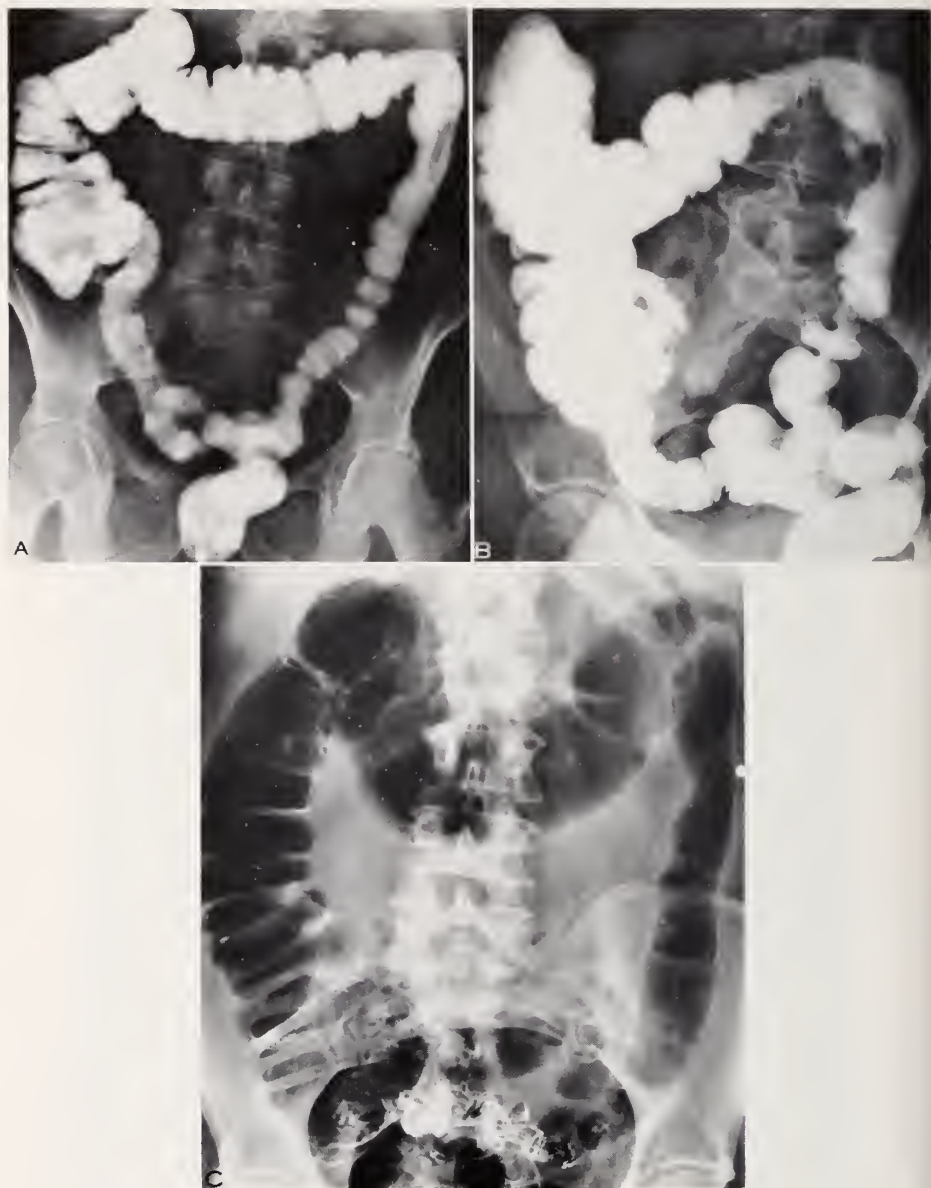
Case 326, Fig. 1A. Left anterior oblique view of the barium filled colon reveals a large segmental area of narrowing involving the distal transverse and the proximal two-thirds of the descending colon. The normal haustral pattern is replaced by thickened edematous folds. These folds in certain areas have the appearance of thick digital markings (arrows). The barium is gray, suggesting a considerable secretion within the affected region. The bowel proximal and distal to the affected region appears normally distensible.

Case 326, Fig. 1B. The right anterior oblique view confirms the presence of a normally distensible right side of colon and sigmoid colon. The affected portion of the transverse and descending colon are again noted.

Case 326, Fig. 1C. After evacuation, the barium that remains in the affected region shows the thickened edematous folds presenting a thick digital impression upon the lumen of the colon (arrows).



Case 326, Figs. 1A-C.



Case 326, Fig. 2A. Repeat barium enema, three months after the initial examination, reveals shortening of the left side of the colon, and some irregular flattening along the proximal descending colon medially. This is due to healing by partial fibrosis. The distal descending has regained normal distensibility.

Case 326, Fig. 2B. In the left anterior oblique projection, the shortened splenic flexure demonstrates narrowing of its lumen and some flattening on its inferior surfaces.

Case 326, Fig. 2C. Air contrast study confirms the normal distensibility of the proximal two-thirds of the transverse colon, and the distal third of the descending colon.

CASE NO. 327

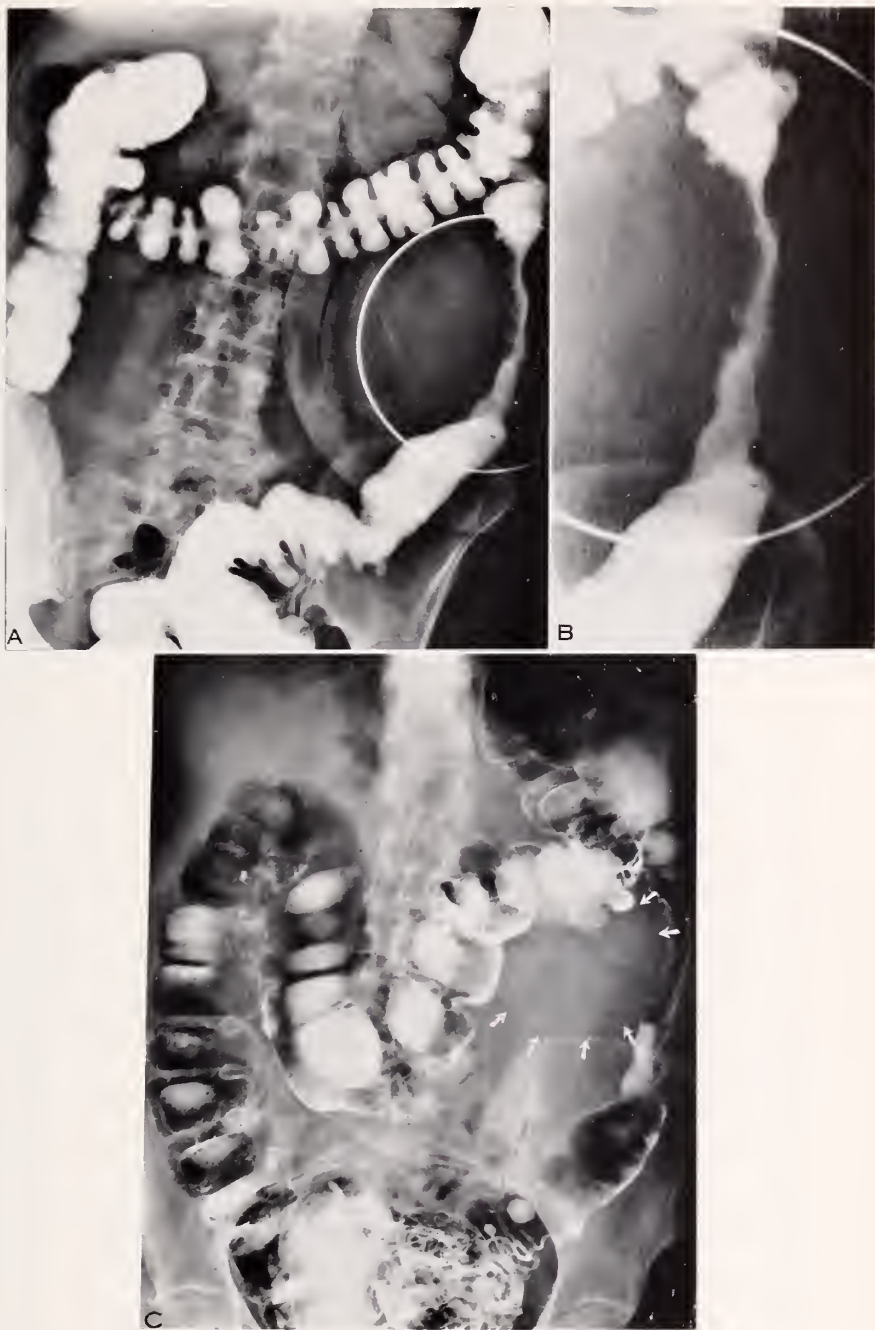
A 65-year-old woman was seen because of the onset of rectal bleeding. There was no abdominal pain, diarrhea, or weight loss. The patient was known to have moderately severe sigmoid diverticulosis, without any history of diverticulitis. Sigmoidoscopy showed a normal rectum and sigmoid, but dark blood was noted above the reach of the scope. Barium enema revealed a well-delineated segmental narrowing in the middle-third of the descending colon (Fig. 1A). The fold pattern was irregular and thickened, but no overhanging edge was seen (Fig. 1B). The lumen was markedly narrowed, but the caliber of the affected segment seemed to change slightly in various stages of the examination (Fig. 1C).

It was noted that there was a large smooth mass in the lower pole of the left kidney, adjacent to the segmental narrowing within the colon (Fig 1C-arrows). Although a definite diagnosis could not be made and a carcinoma could not be excluded with certainty, conservative medical treatment was advised. Three weeks later, a repeat barium enema was performed, and the descending colon showed normal distensibility and caliber throughout its course, confirming the initial impression of a segmental infarction of the colon (Figs. 2A and 2B). The renal work-up showed that the left kidney mass probably represented a benign cyst.

Case 327, Fig. 1A. Barium enema reveals an irregular narrowing of the middle third of the descending colon. The remaining folds appear indistinct and thickened. The lumen is concentric within the affected segment. No nodularity or overhanging edges are noted.

Case 327, Fig. 1B. A spot film of this region shows that the folds are markedly distorted, but that no discrete ulcerations are identified in spite of pressure applied to the region.

Case 327, Fig. 1C. Air contrast study shows that there is some subtle change in the caliber and configuration of the strictured region as compared to Fig. 1A. On this film, it is apparent that there is a large smooth mass in the lower pole of the left kidney (along arrows).



Case 327, Figs. 1A-C.

Case 327, Fig. 2A. Three weeks after the initial examination, repeat barium enema reveals no abnormality of the previously affected segment. Distensibility is normal. No abnormalities of the folds are seen.

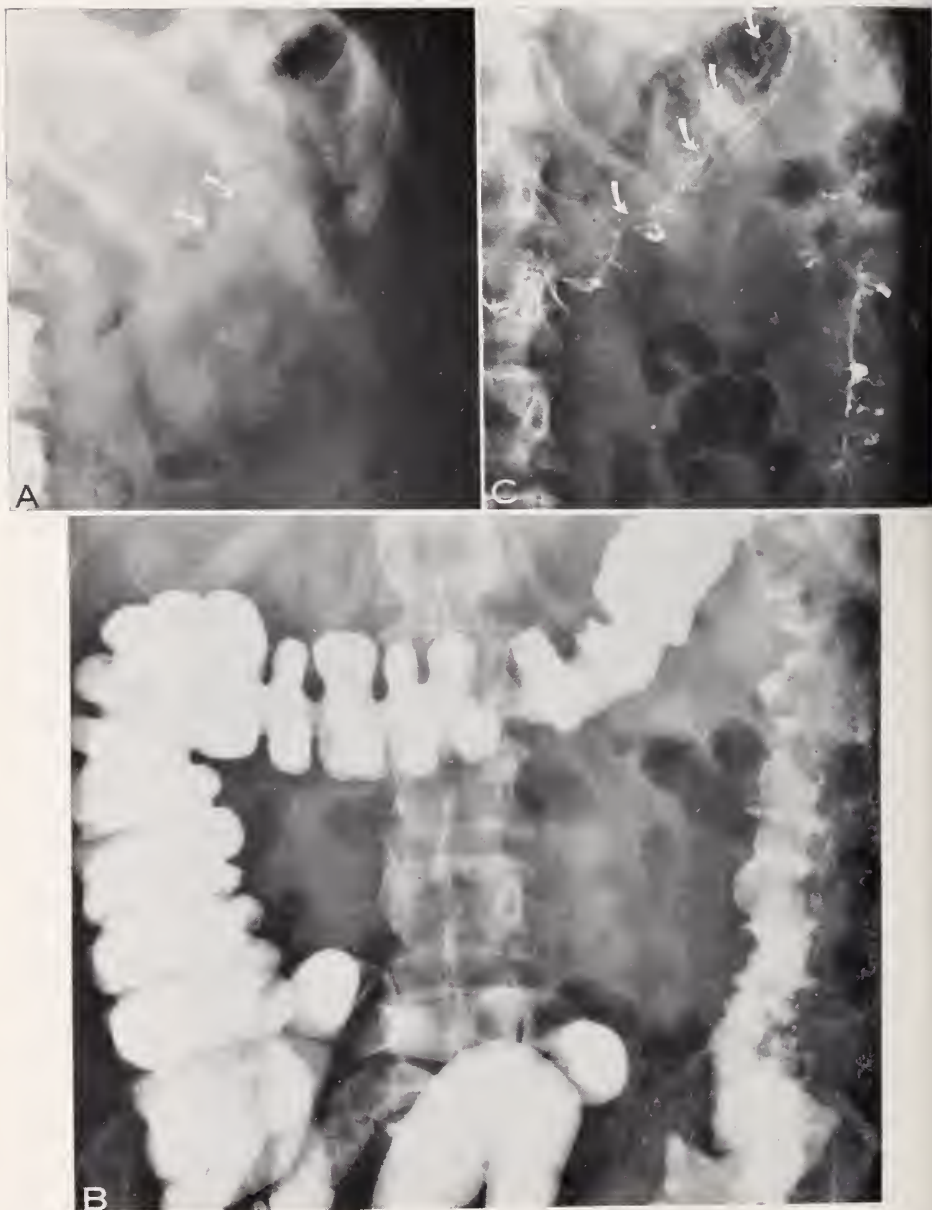
Case 327, Fig. 2B. In the left anterior oblique projection, the normalcy of the previously narrowed segment of the descending colon is again seen.



Case 327, Figs. 2A-B.

CASE NO. 328

A 60-year-old diabetic man was admitted to the hospital with the acute onset of crampy, bloody diarrhea of 12 hours' duration. He was a mild hypertensive, but his vital signs were otherwise normal. There was tenderness in the left lower quadrant, but no masses were palpated. Preliminary radiologic



Case 328, Figs. 1A-C.



Case 328, Fig. 2A. Repeat examination performed one week later reveals the distal cancerous colon to have regained normal distensibility and haustration.

examination of the abdomen revealed a narrow segment of the distal transverse colon outlined by thickened edematous folds (Fig. 1A). Barium enema revealed that the distal transverse colon was slightly narrowed, with loss of normal haustration and flattening of its inferior contour (Fig. 1B). After evacuation, the folds were distorted and indistinct (Fig. 1C). Conservative therapy was administered, and the patient made an uneventful and complete recovery. Repeat barium enema one week after the onset of symptoms

Case 328, Fig. 1A. Preliminary film of the abdomen reveals a narrowed segment within the distal transverse colon. The thickened mucosal folds are well outlined by the air in the lumen (arrows).

Case 328, Fig. 1B. When the colon is filled with barium, the distal half of the transverse colon is noted to be slightly narrowed. The normal haustration seen proximally is replaced by irregular shallow haustra. There is some flattening of the contours inferiorly. Numerous diverticula are noted within the descending colon.

Case 328, Fig. 1C. After evacuation, the thickened folds seen on the preliminary film, as described in 1A, are again noted with the affected segment (arrows).



Case 328, Fig. 2B. The folds as seen after evacuation are noted to have returned to normal.

revealed the affected segment to have regained normal distensibility and haustration (Figs. 2A and 2B).

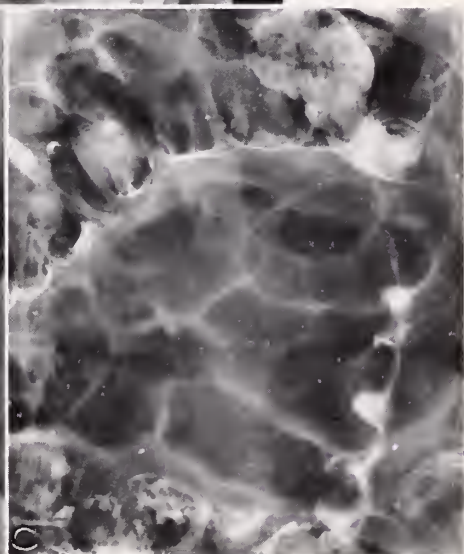
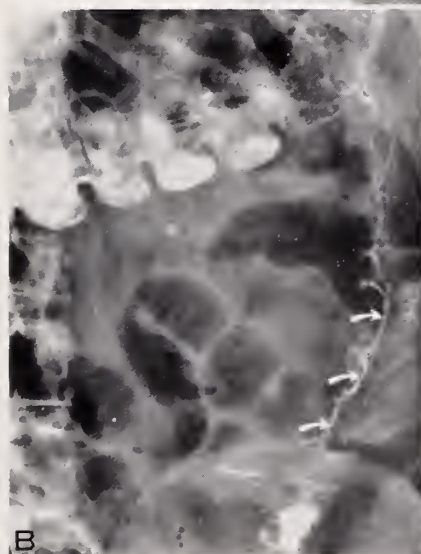
CASES NO. 329-331

In Cases No. 329, 330, and 331, only one examination is available in each instance. Cases 329 and 330 reveal findings suggesting a moderately severe segmental infarction of the descending colon, characterized by decreased distensibility, thickening of the mucosal folds, and some irritability. In Case 331, the process involves the distal transverse and proximal descending colon. There is a concentric narrowing of moderate severity of the involved segment, without proximal dilatation. This indicates healing by partial fibrosis.

Case 329, Fig. 1A. The descending colon is less distensible than normal. Its medial anterior contour is flattened. The folds that are remaining appear thickened, distorted, and somewhat fuzzy in outline. The distal transverse colon appears normal.

Case 329, Fig. 1B. After evacuation, the thickened folds, noted indenting the lumen of the descending colon, appear as large digital marking (arrow). No actual ulcerations can be seen.

Case 329, Fig. 1C. Similar findings are noted on air contrast study.



Case 329, Figs. 1A-C.



Case 330, Fig. 1A. There is narrowing of the proximal portion of the descending colon. The folds are not unusually prominent. No ulcerations are seen.

Case 330, Fig. 1B. With the bowel partially emptied, the folds are noted to be thickened (arrows). No ulcerations are identified.

Case 330, Fig. 1C. Air contrast study reveals a narrowing of the involved segment (between arrows).



Case 331, Fig. 1A. There is marked narrowing of the distal transverse and proximal two-thirds of the descending colon. The haustra are lacking. There is some evidence of proximal dilation. The folds do not appear unusual.

Case 331, Fig. 1B. In the right anterior oblique projection, the constancy of the narrowing of the affected segment is again noted. The lumen has a "pipe stem" appearance.

Discussion

As in other parts of the gastrointestinal tract, the colon reacts to disturbances in both its venous and arterial supply in a predictable fashion. The Roentgen appearance will depend on the severity of the vascular insult and on the interval between the vascular accident and the time of the examination (2). When thrombosis occurs in a major trunk, x-ray examinations are rarely available because of the overwhelming nature of the patient's disease. Most of the available material on vascular colitis either results from vascular thrombosis of a minor branch of the mesenteric system, or vascular compromise due to a volvulus or an incarcerated hernia, or possibly secondary to a generalized vasculitis. When the vascular insult involves a segmental vessel, and the process is slow enough to allow for collateral circulation to take over the blood supply of the involved segment, an interesting pattern can be demonstrated on serial x-rays of the colon. This has now been well described and recognized in the literature (3-5).

On the plain film of the abdomen, during the acute phase, the involved segment of colon reveals air within a narrowed irregular lumen, outlining thickened folds along its walls (Cases 325, Fig. 2A; 328, Fig. 1A). There may also be some proximal colonic dilatation and some degree of paralytic ileus. Although quite rare, cases of localized perforation and segmentally distributed pneumatosis coli have been reported (6). Any segment of the colon may be involved, but most of the cases described affect the left side of the colon, i.e., the distal transverse and proximal descending colon. A few instances of isolated rectal or sigmoid involvement have recently been described (6, 7).

When barium enema is performed during the acute stage of the disease, there is usually evidence of irritability and spasm within the affected segment. The lumen of the bowel is narrowed, and the contours reveal thickened and edematous mucosa, often characterized as thumb-printing, almost in a pseudopolypoid fashion (Cases 325, Fig. 2B; 326, Fig. 1C; 328, Fig. 1C; 329, Fig. 1B; and 330, Fig. 1B.) Discrete ulcerations are rarely demonstrated radiologically. As healing occurs, if fibrosis does not set in, partial or complete reversibility can be noted in as little as seven to ten days (5). This depends on the severity of the initial vascular insult and the subsequent adequacy of the anastomotic blood supply (Cases 325, Figs. 3A and 3B; 327, Figs. 2A and 2B; and 328, Figs. 2A and 2B). When only partial healing has occurred, there is evidence of some segmental area of decreased distensibility, often more pronounced on one portion of the wall than circumferentially. This results in the formation of shallow pseudodiverticula (Case 326, Figs. 2A and 2B.). If fibrosis sets in, it may be seen radiologically as early as three weeks after the initial episode. The findings then are of an area of concentric narrowing, rarely of a severe nature, and without evidence of colonic obstruction (Case 331, Figs. 1A and 1B).

Clinically, there is often the abrupt onset of rectal bleeding and abdominal pain. There is usually no evidence of previous large bowel inflammation. Differential diagnosis is mainly with segmental granulomatous colitis. In the

latter disease, there is often evidence of longitudinal ulcerations or skip lesions. Carcinoma of the colon is usually easily differentiated, in that there is evidence of overhanging edges or extracolonic mass, with evidence of mucosal alterations. In Case 327, because of the unusual short segment involved in the segmental infarction, and the distortion of the affected mucosa, the initial differentiation from a carcinoma was difficult. The changeability of the caliber of the narrowed segment helped to make the correct evaluation. It was also thought that the renal mass, being immediately adjacent to the affected segment, might represent colonic invasion from a hypernephroma. Against this diagnosis, was the exquisite smoothness of the mass and the lack of nodularity or thickening of the wall of the colon. It is possible that the renal cyst contributed to a poor blood supply to the adjoining colon, precipitating a segmental infarction. This has been reported previously in the literature.

In the differentiation between ischemic and granulomatous colitis, the most important feature is the rapid reversibility of the Roentgen finding in the former, the colon often returning to a normal appearance ten days after the initial episode.

Acknowledgments

The Editors wish to thank Dr. Robert L. Segal, Dr. Arthur H. Aufses Jr., and Dr. Arthur M. Figur for their permission to publish Cases Nos. 325, 326, 327, and 328 respectively.

References

1. Marston, A., Pheils, M. T., Thomas, M. L., and Morson, B. C.: Ischemic Colitis, *Gut* 7:1, 1966.
2. Hannan, J., Jackson, B. F., and Pipak, P.: Fibrosis and Stenosis of the Descending Colon and Sigmoid following Occlusion of the Inferior Mesenteric Artery, *Amer J Roentgen* 91:826-832, 1964.
3. Schwartz, S., et al.: Roentgenologic Features of Vascular Disorders of the Intestines, *Radiol Clin N Amer* 2:71-87, 1964.
4. Marshak, R. H., Maklansky, D., and Calem, S. H.: Segmental Infarction of the Colon, *Amer J Dig Dis* 10:86, 1965.
5. Marshak, R. H., and Lindner, A. E.: Vascular Disease of the Small Bowel and Colon. In Margulis, A. R., and Burhenne, H. J., ed.: *Alimentary Tract Roentgenology* C. V. Mosby Co., St. Louis 1967 2:1144-1156.
6. Marshak, R. H., and Lindner, A. E.: Ischemia of the Colon, *Seminars Roent* 3:81-93, 1968.
7. Farman, J., Betancourt, E., and Kilpatrick, Z. M.: Radiology of Ischemic Proctitis, *Radiology* 91: 302-307, 1968.

MOUNT SINAI SCHOOL OF MEDICINE

OF THE

CITY UNIVERSITY OF NEW YORK

THE PAGE AND WILLIAM BLACK
POST-GRADUATE SCHOOL OF MEDICINE

ANNOUNCES ITS POST-GRADUATE COURSES FOR
SEPTEMBER-DECEMBER, 1969

COURSES FOR GENERAL PRACTITIONERS

Integration of Contemporary Internal Medicine at Bedside Stanley G. Seckler, M.D., Irving Chapman, M.D. and Gertrude Oxenberg, M.D.

September 3 through September 26, 1969, Wednesday and Friday, 1:00 PM to 4:00 PM

Otolaryngology for Non-Otolaryngologists Karl M. Morgenstein, M.D., Joseph L. Goldman, M.D. and Associates.

September 3 through December 17, 1969, Wednesday, 4:00 PM to 6:00 PM

Teaching Conferences for Staffs of Medical Clinics of the Mount Sinai Medical Center Leonard Stone, M.D. and Associates.

October 1969 through May 1970

Computer Analysis of the Electrocardiogram and Vectordiagram Leon Pordy, M.D., Harry L. Jaffe, M.D., Kenneth Chesky, M.D. and Charles K. Friedberg, M.D.

October 2nd and 3rd, 1969, Thursday and Friday, 9:00 AM to 1:00 PM and 2:00 PM to 5:00 PM

Differential Diagnosis in Radiology of the Chest Coleman B. Rabin, M.D. and Bernard S. Wolf, M.D.

October 6 through December 29, 1969, Monday, 5:00 PM to 6:00 PM

Orthopaedics in Infancy and Childhood Robert S. Siffert, M.D. and Staff

October 7, 14, 21 and 28, 1969, Tuesdays, 3:00 PM to 5:00 PM

Clinical Psychiatry for the Older Patient Alvin Goldfarb, M.D.

October 7 through November 11, 1969, Tuesday, 12:30 PM to 2:00 PM

Differential Diagnosis in Gastrointestinal Radiology Richard H. Marshak, M.D. and Mansho T. Khilnani, M.D.

October 7 through December 9, 1969, Tuesday, 5:00 PM to 6:00 PM

Clinical Psychiatry for Medical Practitioners and Non-Psychiatric Specialists M. Ralph Kaufman, M.D., Harry Diener, M.D., Hans J. Kleinschmidt, M.D. and Associates

October 8 through June 27, 1970, Wednesday and/or Saturdays, 9:00 AM to 12:30 PM

Follow-Up Seminar in Basic Psychiatry for General Practitioners, Internists and Medical Specialists Hans J. Kleinschmidt, M.D.

October 22, 1969 through June 24, 1970, alternate Wednesdays, 8:30 PM to 10:30 PM

Clinical Chest Diseases Louis E. Siltzbach, M.D., Robert S. Litwak, M.D., Irving J. Selikoff, M.D. and Associates.

November 3 through November 7, 1969, Monday through Friday, 9:00 AM to 12:00 Noon

Recent Advances in the Management of Renal Failure* Eugene Schupak, M.D., Marvin Goldstein, M.D., Lionel Mailloux, M.D. and Lewis Burrows, M.D.

November 11 through December 30, 1969, Tuesday, 8:30 AM to 12:00 Noon

Care of the Patient with Acute Stroke* Lawrence H. Wisham, M.D., Lawrence I. Kaplan, M.D. and Associates

November 12, 1969, Wednesday, 9:00 AM to 3:00 PM

* To be given at the City Hospital Center at Elmhurst, New York.

In Memoriam

MARTIN C. ROSENTHAL, M.D.

1922-1969

On March 27, 1969 Martin Rosenthal died, ending abruptly and prematurely at the age of 47 the life of a fine physician and dear friend of The Mount Sinai Hospital.

Dr. Martin C. Rosenthal graduated with highest honors from Columbia College just before World War II. During that war he served as a medical student in the military program at New York University Medical School. His internship in 1945 at The Mount Sinai Hospital started a relationship with this institution which continued to his untimely death. He completed his hematology residency and research fellowship here and went to Boston, where he worked as a Senior Runyon Clinical Research Fellow of the American Cancer Society, and as an instructor in medicine at Pratt Diagnostic Hospital and Tufts College Medical School. There he sharpened his talents in the academic and clinical aspects of hematology. It was in Boston that he also enjoyed those early years of his satisfying marriage to Elaine, and it was there that he developed cultural interests in music and art.

Martin returned to New York and to The Mount Sinai Hospital in 1953 to continue his research fellowship, his writing, his teaching, and his studies of hematology. His research contributions on the coagulation of blood were published in more than 30 articles in various journals in the medical literature. Many of these papers were written with colleagues who remained close friends as well as collaborators throughout his years in practice. As Medical Director of the National Hemophilia Foundation, he widened the scope of his contributions to the stricken. As a private practitioner, consultant and clinician, Martin was masterful. Along with his association with The Mount Sinai Hospital, he was also Consultant Hematologist to other hospitals, including Vassar Brothers Hospital in Poughkeepsie, Elizabeth Horton Hospital in Middletown, St. Luke's Hospital in Newburgh, and City Hospital at Elmhurst. When one physician heard of Martin's death he spoke for many, and sorrowfully said, "I've lost my crutch." Martin combined the characteristics of the sympathetic physician with those of the sophisticated scientist and consultant. At his funeral services they sat admixed in the crowded chapel, leukemias and anemias, physicians and technicians, all saddened by their loss.

In recent years Martin developed a renewed interest in sailing, and he became a devoted student of navigation and seamanship. Much of his leisure was spent at the tiller in Long Island Sound, always with his wife at his side, and often with his children.



MARTIN C. ROSENTHAL, M.D.
1922-1969

Martin was a member of learned societies including Phi Beta Kappa; American Society of Hematology; International Society of Hematology; American Federation for Clinical Research; National Hemophilia Foundation, which he directed; and The World Federation of Hemophilia, for whose medical board he was Secretary. At the Medical School he was Associate Clinical Professor of Hematology.

At his death, patients lost their good physician, doctors lost their hematology consultant, hemophiliacs lost their champion, and The Mount Sinai Hospital lost a dear friend.

NORMAN SIMON, M.D.

for the

EDITORIAL BOARD

Currents in Medical Education in the United States

HANS POPPER, M.D., PH.D.†

Social and educational goals are being redefined all over the world in response to unrest in the population, especially among the youth. This results also in a search for new patterns in medical education and in an attempt to balance antagonistic, but not necessarily undesirable ideas. In our country, this search has led to several specific developments.

1) The emotional dissatisfaction with university policies among students and young faculty members has agitated the public and the mass media. The climate of dissatisfaction is less aggressive in medical schools, where the students are brighter and better educated today than in previous generations, as the result of superior premedical teaching. They challenge the relevance of what they are presently being taught. This dissatisfaction with the establishment, not always well articulated, has led to two constructive developments, namely: a) a greater concern of the medical student for the welfare of people, particularly of the economically and socially disadvantaged; and b) an increasing participation of the students in the organization of medical education. We are looking for a way to make this participation more effective without encroaching too much on the students' time, and without putting too much responsibility on a transient school population. In our new school, this desire for participation has been most beneficial in that our students consider themselves key factors not only in the outcome, but also in the design of an experiment in medical education.

2) Society enters into the conduct of medicine through its legal arm, the government. Much of what in other countries is the responsibility of government, the American tries to preserve for voluntary organizations, representing, for example, physicians, nurses, or medical schools. Therefore, physicians have had an overwhelming influence on medical practice and on medical education. For instance, they have emphasized basic research in the development of medicine. This has resulted in a record which most of us consider enviable. Nevertheless, the feeling prevails that the progress in biology has not done all that is possible for the medical care of the entire population; this has led to a surveillance of medicine by sociologists and bureaucrats, with an attempt to introduce measures to improve the delivery of medical care under governmental sponsorship. This influence is not coercion, but takes the form of grants in support of medical research and teaching.

3) The dissatisfaction of the general population with medical care is ag-

From a presentation at the International Symposium on the Restructuring of Medical Schools in Milan, Italy, November 24, 1968.

† Dean for Academic Affairs, Given Foundation Professor, and Chairman of the Department of Pathology, the Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

gravated by its increasing cost, which has become prohibitive even for the middle class. The cost of health care in America at present represents six percent of the Gross National Product (1). Despite this expenditure, the nation does not have sufficient physicians, and particularly lacks physicians of first contact—the general practitioner, or family doctor. This dissatisfaction is augmented by an increased awareness in the population at large about medicine and its potential.

4) New ideas in medical education are being offered in confusing array in publications, conferences, and professional organizations devoted to research in medical education. Although this “great debate” is still going on, new experiments in medical education are already under way in the old established, and in the new developing schools in the United States. These experiments reflect a third revolution in medical education in this country (2).

The first, the “academic revolution” in the early part of the last century, replaced apprenticeships with practicing physicians with formal education in schools, either university-affiliated or independent, thus accepting in America the traditional system of Continental Europe.

The second, the “biologic revolution” at the turn of the century, was expressed in the founding of the Johns Hopkins Medical School in the image of the German universities, and even more important, in the changes following the Flexner report (3). Flexner’s review of medical education, published around 1910, was responsible for the biologic basis of medicine becoming the cornerstone of teaching. It also induced the creation of a rigid curriculum with lockstep education, in contrast to the experience of the student before medical school and, especially, to the freedom of the European medical student. The medical graduate was expected to be an effective physician after one year of obligatory hospital work as an intern. Flexner’s recommendations were enforced by voluntary organizations which eliminated many substandard medical schools. A four-year curriculum, two years’ preclinical and two years’ clinical study, was preceded by three or four years of college, which in part provided compulsory, and rather uniform premedical courses, while the rest of the college time could be devoted to various endeavors, such as biologic studies, social studies, or humanities. In view of the minor variations of the curriculum throughout the schools, transfer from one school to another was academically easy, though seldom practiced.

The third, the “sociologic revolution,” under way at present, causes great variations in curricula throughout the country. It reflects several factors, namely: a) the realization that behavioral and social elements deserve more emphasis in the training of physicians; b) the demand that the delivery of medical care should be what the population wants; and c) medical knowledge has become so large that it is impossible to develop a universally trained physician in four or five years. Under the present system, therefore, physicians can become independent practitioners upon graduation only in exceptional

cases. Few physicians will be fully trained in their respective fields before thirty years of age, and some considerably later.

A review of the present currents of medical education in the United States against this background of an intellectual and sociologic revolution, and against the question of relevance, can be made under three headings: 1) prediction of the type of practice of medicine in future decades for which the student has to be trained now; 2) the various trends and conflicts in medical education recognizable now; and 3) the specific attempts to resolve in practical fashion the frequently antagonistic forces.

1) Any prediction as to the future practice of medicine will doubtless appear naive within a short time. Nevertheless, it may offer some guidance in the planning (4). The present trend towards disappearance of the general practitioner or family physician, furthered by the emergence of complex procedures and equipment, is associated with an increasing depth in the ever shrinking area of the specialist, the main product of many of our medical schools. If this development should not be altered by government regulations, measures will have to be taken to provide for the real medical needs of the population. If no family physicians with presumably less training and less dependence upon laboratory equipment are developed, then health professionals without the M.D. degree and with shorter training periods may have to take over some of the physician's functions and, thus, lengthen his arm. However, instead of being independent practitioners, as they are in some countries, they will, in the United States, be members of a health team where professionals with different degrees of training will work together under the supervision of physicians. They may be the health workers of first contact, for instance, in house calls or outpatient clinics, with supervision being facilitated by technical advances, such as two-way radio or television, which may make expert opinion from the medical center available in distant locations. This health team, with physicians trained in the distribution of medical care at its head, may be similar in organization to that in our laboratories or in industry. This system, which is being planned in the United States, provides opportunity for upward mobility for the lower members of the health team. For instance, the technician or community health worker could become, with additional schooling, a graduate physician; or the laboratory technician, a Ph.D. In such a system, some of the graduates of the medical schools would become highly trained specialists in somatic areas; others might become psychiatrists assisted by specially trained health personnel, such as psychiatric social workers; while other M.D. graduates may be social scientist physicians (5), or community medicine specialists, concerned with organization of the delivery of medical care and with research in its improvement. A fourth category would be clinical or basic science research workers cooperating with the paramedical scientists having Ph.D. degrees in biological, physical, or social sciences. If such a system should develop, members of this complex health team should work and be trained together

in the same school or branch of a university, so that the medical school would become a health science school.

2) Turning to the present evolution of medical practice and medical education, several specific trends have to be listed supplementing those mentioned in the introduction. They frequently reflect antagonistic and synergistic forces, with balance of these polarities being the goal in medical education, and particularly in curriculum design.

a) Knowledge relevant to medicine is increasing in an explosive fashion as a result of the extension of our experience and, even more so, as a result of the development of complex chemical and physical methods of measurement. This trend is opposed by three factors: the unity of biology; the quantitation of biologic observations; and the storage, as well as analysis, of observations by computer techniques.

The unity of biology (6) implies that biologic processes in all living organisms may be similar; for instance, the study of the metabolism of virus or bacteria assists in the understanding of processes in man, and has thus provided answers to therapeutic problems, as in the use of antibiotics. This unity of biology permits replacement of the teaching of facts by that of principles, which are better remembered. The unity of biology also means the use of similar techniques and models in the various, traditionally separate, basic science departments of the medical school, such as anatomy, physiology, biochemistry, pharmacology, microbiology, and pathology. Unity of biology thus militates against the traditional structure of the medical school, but also favors integrated teaching.

The refinement of physical, chemical, or fine structural measurements assists in the recording of observations on patients in objective terms, and moves aspects of clinical diagnosis and prognosis from intuition to firm prediction.

The recall of stored information and its analysis by computers is applied increasingly in clinical diagnosis, and in the monitoring of various conditions. For instance, in the postoperative stage, the combination of vital signs and biochemical alterations may be integrated into alarm signals before the individual finding reflects a dangerous level. Computer techniques are also used in the organization of patient care in hospitals and, most important for our discussion, in teaching machines permitting self-education of the student; they will not, and should not, however, ever replace the human brain.

b) A clinical science is being developed which applies at the bedside an approach, accuracy, technical sophistication, and particularly intellectual discipline which until now have characterized primarily investigations in the experimental laboratory. Cardiology has led the way in this respect, but similar methods are now being used throughout all of medicine. There is a conflict between clinical science concerned with problems, and clinical art, which is concerned with the single patient and is based on intuition rather than objective reasoning. The reconciliation between the clinical scientist and the

clinical artist, the physician primarily concerned with the single patient before him, is a problem for the individual clinical teacher. It is also a major educational problem for the school at large, since the student is in a dilemma whether to emulate the successful practitioner or the famous clinical researcher.

c) Therapeutic procedures, both pharmacologic and surgical, are becoming more potent. However, the effect of a drug is, as a rule, not specific enough to avoid changes in structures or metabolic pathways which are not its primary target. Untoward side effects, therefore, cannot be avoided and may threaten the patient's life. Similarly, as surgery moves from the simple removal of organs to alterations of physiologic conditions, as in transplantation, unpredictable effects result which can often be evaluated only in human experiences. The indication for a therapeutic procedure in the individual patient becomes thus a serious ethical problem. The medical student has not only to learn the biologic basis of these procedures, but also guidelines in the human problem of the selection of the patient.

d) The notion is being doubted that the biologic basis is the most effective key in understanding the cause of disease, and that correction of the biologic abnormalities in somatic disease is the best way to prevent or treat it. The suspicion is raised, though not confirmed as yet, that emotional, social, and environmental (not necessarily economic) factors explain why some persons are afflicted by a disease, and others not. The fact, therefore, dawns on an increasing number of laymen and physicians that genetic predisposition and exposure to injurious agents do not alone determine why a person becomes sick. These considerations of a psychosomatic basis of many diseases are at present supported by statistical study of patients entering hospitals. This opens up vistas as to etiology and incidence of disease, which are not related to readily understandable biologic, and even psychobiologic principles.

e) Concern for the dignity of the patient is increasing. Therefore, human and community considerations require increased emphasis as compared to the biologic basis of disease. The image of the physician as a priest-like being endowed with mystic powers is declining as he is becoming a technically skilled specialist surrounded by complex machines. Attention is, therefore, focused upon the reaction of the patient to medical care beyond the management of the presenting disease. The population demands continuous medical attention, comprehensive as far as the single patient, as well as his family, are concerned. They want this, in addition to the episodic attention given the inpatient in the hospital. Equipped with increasingly more elaborate equipment, the hospital thus develops into a major health center for family care, supported by satellite community health stations near the patient's domicile. With such health stations, travel to the major centers is necessary only when highly specialized knowledge or complex equipment is required. Between the university medical centers and local health stations is interposed the community hospital, smaller than the center and intermediate in skills and equipment. While the primary functions of the medical school have been

traditionally teaching and research, patient service in the institution has been considered essential in support of these primary functions. The evolution extends the service functions into the community and its health facilities. Yet, the primary function of the medical school in the community should not be to give service, but to teach its medical and health professional students, and to perform research to establish the best possible system of delivery of medical care. But any attempt to restrict community services to the level required for teaching and research encounters the strong demands of society for action in resolving community health problems. Discussions in the United States have so far not led to an agreed balance.

f) The graduate programs of the universities leading to Ph.D. degrees are based on the traditional university principle of striving for full development of the student's intellectual potential. Thus, the graduate schools are student oriented, dedicated to the quest for truth; thoughts are emphasized rather than facts. Trade schools, in contrast, teach primarily applied sciences, and thus are oriented towards performance. The medical school strives to be a graduate school. But physicians have to apply skills and utilize facts derived less from rational reasoning than from empiric observations, which have to be memorized, rather than understood. This introduces trade school principles into medical schools and creates another conflict.

g) The recognition that the young physician after graduation requires considerable additional training to become an effective independent practitioner, has led to increased educational structuring of the postgraduate hospital years, designated as internship or residency. Originally, the young physician was an apprentice in these years, learning more by experience than by supervision. At present, these young physicians are considered more and more as students, requiring organized instruction to make them effective and to avoid waste of their time by educationally less rewarding service. These additional "student" years after graduation with an M.D. degree are presently controlled by the hospitals. However, an attempt is being made to make the medical schools responsible also for these years, adding to the university's responsibility.

h) The number of physicians needed in the future depends on the prevailing system of medical care, and particularly on the function of the physician of first contact, the general practitioner. The great advances of biology in medicine and the miraculous therapeutic successes induce many students to select narrow specialization as a career, not only to treat his patient more effectively, but also to conduct research in an exciting area. In a free society, this results in an overproduction of specialists without relation to society's needs, and a scarcity of general practitioners. This is the case in the United States, where strenuous efforts are being made to increase the output of general practitioners. The awakening social conscience of the students may help to correct this disproportion, but in my opinion it will probably not do so, despite all attempts of schools to make general practice more attractive. Recruitment of medical students from various social strata and geographic

locations is attempted, together with the recommendation to alter admission requirements of the medical school by considering future social usefulness more important than demonstrated abilities at the time of entrance. This may relieve the scarcity of general practitioners temporarily, but as the desirable intellectual achievements of such groups catch up with their potential, the desire of such students to return to their area of origin as general practitioners will fade. This is observed in the developing countries all over the world, where most of the physicians congregate in the population centers and shy away from the villages where they are mostly needed. The solution to this problem is not in sight. The reorganization of medical care by health teams might remain the only answer in the more distant future.

i) Surprisingly, some men successful in biologic and clinical research and teaching are embracing the new tenet of the "sociologic revolution in medical education," and thus almost question the relevance of their own endeavors, unless they are tempered by considerations for the individual person and for the community at large. The standard bearers of this thinking compose three groups: (1) the professional medical educators; (2) the young Ph.D.'s in medical education who are instructors in the preclinical sciences; and (3) some older leaders in clinical and biological medicine. In the latter group, serenity favors breadth of thinking, but age also removes them from the cutting edge of research in medicine (to avoid the hard word senility), and may turn them toward sociology, which does not require the exactness of biologic science. These three groups, together with the students, and even with community forces outside of medicine, will, however, not be effective until the broad masses of successful practicing physicians join in the sociologic revolution in medicine.

3) To be prepared for the predicted system of medicine, to deal with the listed trends, and to find an equilibrium between the multitudes of polarities, several specific devices or solutions are being designed in America. They represent part of the medical experiment conceived with ingenuity, and sometimes with compulsion bordering on belligerency. Unfortunately, the only indication of the success of the experiment will be the performance of the future physician, which we cannot evaluate until the end of this century.

a) In the design of the medical curriculum, integration has become a key word. It has to be considered at least on three levels.

One is the integration of the teaching space, particularly in the sciences basic to medicine. The multidisciplinary laboratory is now widely used. There, all types of laboratory exercises are carried out by the students, sometimes including even gross anatomic dissection. The instructors come to the students, rather than the students circulating through different laboratories and lecture halls. It provides the students with a home base for study, free of fixed working hours, thus improving their study habits. The architectural design of effective multidisciplinary laboratories is still a difficult problem.

A second integration concerns the connection of basic science with clinical medicine, and of both with the nonbiological aspects of medicine. In almost

all American schools, students are now exposed very early to patients, by direct contact, or by clinical demonstrations. This brings home to the student the relevance of basic science in the management of patients; it emphasizes the nonbiologic aspects of medicine in order to avoid the loss of human concern during the abstract studies of basic science; and it teaches the student early to be at ease with patients. More difficult is the recall of basic science information during the clinical years. This recall is best structured around pharmacology and pathology.

The third integration involves the subject matter which is being taught simultaneously from the point of view of morphologic, functional, and clinical aspects, with the emphasis on organ systems and pathological processes, rather than on disciplines. It results, thus, in interdepartmental teaching, and reduces the sovereignty of the individual medical school department which had been accustomed to organizing its own course in a block time. Integrated teaching is far more difficult. It requires time-consuming planning by a committee representing the various departments, which should also include students. On such a committee, students who already have taken the respective courses are more effective than those who have yet to take them. Integration requires a very large teaching staff, particularly for combined laboratory exercises which are organized by several departments. It is made difficult by the fact that today's textbooks are discipline—rather than organ—oriented. Thus, a specific syllabus has to be prepared, taxing the time of the faculty. However, subject matter integration avoids harmful duplications, reduces teaching time, and particularly stimulates student interest, and sometimes faculty enthusiasm in teaching.

b) The most difficult problem in the selection of teaching material is the identification of the skills and information required of every physician. They represent what may be called "core curriculum." This essential skeleton of information needed by every physician has to be separated from the practical and theoretical knowledge required by the specialist, and from the type of teaching which is directed toward the development of student intellects and study habits. The student should be encouraged to continue study after completion of his training to learn the emerging aspects of medicine pertinent to his particular career. In this second type of study, apart from the core curriculum, and designated as "elective studies" or "free curriculum," maximal flexibility is essential. There seems to be agreement that the core curriculum should provide less knowledge than is offered now in the total curriculum, especially as to basic science information. The present obligatory laboratory periods can probably be significantly reduced as the advance in techniques moves much laboratory responsibility from the physician to the technician. The free curriculum, by contrast, is usually a study in depth in one area, which might better develop the student than the previous lockstep arrangement. It can be carried out in the laboratory; in the clinical area; or in social fields, and thus may help the student to test his own interests and capabilities.

Since the student in the free curriculum is, in effect, a graduate student, the role of tutors and of research becomes a problem. While some feel that research may assist in the development of the decision making required of any physician, others, like myself, are opposed to obligatory research. Most important, the free curriculum permits a "multiple track system" varying with the individual student.

c) Several plans are at present being tried out to reduce the years of training. For instance, combining college and medical school education might reduce the total number of years required. This is acceptance of the system of Continental Europe. The successes of these experiments are mixed because of the varied maturity of the students. More effective probably, is the attempt to foster early recognition of career goals by the students, exemplified in the "multiple track system". All students may take the same core curriculum, either compressed into the early years of medical studies or spread throughout all years. In addition, extensive free curriculum or elective time permits preparation for a specific future career, with the demands varying according to the student's intention to become a general practitioner; a clinical specialist; a psychiatrist; a specialist in community medicine (in part derived from a community health worker who subsequently became a physician, and probably to a greater part, from medical students fascinated by social problems); or a researcher in clinical or basic science. For the latter groups, a combination of M.D. and Ph.D. study is being tried. The scope of the clinical specialties is undergoing a change, in that the same organ orientation and the same profound knowledge of applicable basic science that is required of the internist, is required of the surgeon. Therefore, the same physician begins to carry out both the medical and the surgical management of his patients. This has been the case in ophthalmology, for example, and is now spreading to combinations of cardiology with cardiologic surgery, or neurology with neurosurgery. The success of this multiple track system will to a great degree depend on the success in making the years after graduation from medical school into additional school years.

The mechanics of an early career decision should not stand in the way of changing the "tracks" in the student; the postdoctoral year, and even the core curriculum should prepare for late changes, for instance, when the successful clinician and researcher should eventually become an administrator, who then has to take into account social problems.

d) The educational impact of ongoing changes in medical practice is hard to evaluate, particularly since, at least in the United States, statistical figures as to the optimal organization of medical practice, and as to medical manpower needs are at this time not available. An effective relationship among the individual physician, community health stations as outpatient clinics, community hospitals, and the university teaching hospitals has not yet been worked out. A major organized attempt is the regional medical program, devoted at present mainly to heart, cancer, and stroke, where the

outlying community health stations and the community hospitals serve as satellite units to the teaching hospitals in the flow of patients requiring specialized medical treatment. This organization is intended to bring the results of recent advances in medicine rapidly to the entire population. If successful, it might change the pattern of medicine, by, for example, increasing the number of salaried full time physicians replacing the free practitioners. The medical school would have the facility to follow patient flow.

Another important development is the disappearance of the charity patient who used not to be able to choose his own physician, and thus was more easily utilized in teaching and research than the patient who enters the hospital or the outpatient clinic under the care of his own physician. The latter type of patient is not easily used in the teaching of medical students and house staff, but it is an advantage to the students to learn on the type of patient they will be dealing with mainly in practice.

e) The mechanics of teaching are undergoing extensive experimentation. Reduction of the class size has been a result of the "biologic revolution," and has made possible close contact between instructors and students, and a reduction of formal lectures in favor of small group discussions and seminars which enhance student participation. The clinical lectures have been almost completely replaced by bedside teaching. Increasing expertise in the psychology of education, and the application of teaching machines and audio-visual aids are making themselves felt. If lectures are preceded by distribution of detailed outlines with schematic sketches and literature references, student participation is promoted. However, at present the small class size is challenged by the pressure of the community for more physicians.

f) The limitation of places for medical students (in contrast to most schools in Continental Europe) increases the responsibility in student selection, which in the United States has been based upon: (1) grades in college; (2) recommendation by college teachers; (3) nationwide examinations to equalize differences in various colleges; and (4) personal interview. This system has worked successfully, as witnessed by a relatively small loss of medical students during the school years. It has forced many who wanted to study medicine to change their goal or to study abroad. This system discriminates, however, against students from intellectually disadvantaged social or geographic areas by giving preference to applicants from intellectually motivated surroundings. Although an elaborate scholarship program in the United States theoretically abolishes financial limitations to the study of medicine, the present selection of students has greatly favored middle and upper class students. This discrimination is not only unjust, but also deprives the country of effective physicians, whose potential is not apparent at the time of admission to the medical school. This situation requires sensitivity on the part of those responsible for admission. It requires also the mechanics for either additional training of promising candidates before medical school, or prolonged training in the school for the student with little achievement but intellectual and social potential.

g) Evaluation of the student's ability and performance is a crucial part of his education, whether or not it is expressed in grades, and whether it is done by oral or written examinations. Examinations serve, in effect, four purposes. The one considered essential all over the world is the qualifying examination of a physician, which serves to protect society against inadequately trained practitioners. Secondly, they assist instructor and student in spotting weaknesses before they become incorrigible, and at the same time help to guide the student's career. Thirdly, they provide information to the instructor about the efficiency of his teaching. And fourthly, they stimulate the student to prepare himself. The last three purposes are recognized as important in lower education everywhere, but are not considered important in medical education in Continental Europe, because of the assumed maturity of the student. By contrast, in the United States, they are highly valued in medical education; repetitive examinations are frequent, and elaborate grading systems are developed. Moreover, complicated written tests are worked out by specially trained psychologists, and objectivity in testing is accomplished by mechanical devices. The examination system thus represents probably the greatest contrast between European and American medical education. While the American system provides useful supervision and guidance, the relatively small classes introduce pernicious elements of competition between students. A reevaluation of the examination system is under way, which includes withholding information about grades from the student even if they are recorded, or withholding the student's name from the faculty so that the faculty knows the overall results of the test, and the student his potential weakness. Obviously, comprehensive qualifying examinations can never be abolished in a field like medicine, but it might suffice to simply distinguish between passing and failure and to base the guidance of the student upon personal contacts, in electives, for example, which might better test capacities than the rigid core curriculum. There is at this time no consensus about the optimal examination and guidance system, and feedback information from the students is most useful in this quandary.

h) The relation between medical school and university in educational and financial aspects, as well as from point of view of public service has emerged as a problem, not foreseen a few decades ago. There is little argument about the educational interdependence between both. Nonbiologic disciplines, represented only at the university, such as sociology, economics, mathematics, and psychology have become important in medicine. Moreover, in physical sciences and particularly engineering, the university has the strengths necessary to teaching and research in the medical school. At the same time, scientists at the university in these and other fields are using the medical school and its hospital as their teaching and research laboratory.

The economics of university education are complex. The most difficult problem involves the medical school, which is the most expensive component. However, it is the university component which, by selling its medical services, may be partly self-supporting. The public sector, representing city, state,

or federal government, and the private sector, depending mainly on voluntary philanthropic contributions, vary in their relative support of universities, depending upon the state of the economy and the prevailing political philosophy. An interesting mixture exists at our own medical school, which is privately endowed and leans heavily on the private sector for its finances, but is organizationally part of a public university. While in the past the privately endowed schools had more prestige, the tax supported schools have come up on the ladder of prestige, but have so far not reached the private schools. Governmental financial support is important in the private as well as the public schools, and so far has had hardly any influence upon the principles of education. The government supports: (1) research, including training for research; (2) loans to student; and (3) to a small degree, specific educational activities. The "sociologic revolution," however, influences privately and publicly endowed schools equally.

I have referred repeatedly to the changing roles of the university, which is best defined as a community of scholars. There is consensus in the United States that it has to get out of its own walls, but there is no agreement as to how far (7). Everybody believes that the university should attempt to work out solutions to the social problems, not only of medical care and of health, but also of others, such as transportation or city organization; but, to what degree the universities should serve in the execution of the solutions, is a question.

Projection

At a time of change in medical education, the question of relevance of the material taught is uppermost in our minds. This change is reflected in the development of new curricula, but we have no yardstick yet to judge their results. Therefore, mechanics for continuous changes of the curriculum with flexibility is essential. The participation of the student in the conduct of medical education, desired equally by students and faculty, is crucial and particularly useful in the curriculum redesign. The preservation and expansion of the enthusiasm of both groups is today the main obligation of the administrations of medical schools, universities, and government. In the excitement of that change we should not, however, forget that the "biologic revolution" in medical education at the beginning of this century was based upon, and preserved the fruits of the "academic revolution" of the middle of the last century. Similarly, the present "sociologic revolution" should be based upon the progress in biology and preserve it. Thus students, faculty, and administration share the responsibility to assure that the "sociologic revolution in medical education," with its potential emphasis on quantity rather than quality, does not interfere with the very foundation of education, namely excellence.

References

1. Piel, G.: Commencement Address: Cornell University Medical College, June 5, 1968.
2. Lippard, V. W.: How Should the National Board Respond to Changing Patterns of

- Medical Educations?, The National Board Examiner 15:April 17, 1968 (Survey of Pathology in Medicine and Surgery 4:91, 1968).
3. Flexner, A.: Medical Education in the United States and Canada: A report to the Carnegie Foundation for the Advancement of Teaching with an Introduction by Henry S. Pritchett, The Foundation (reproduced in 1960).
 4. Popper, H.: New Objectives in Medical Education. *Ann N Y Acad Sci* 128:473-479, 1965.
 5. Funkenstein, D. H.: Implications of the Rapid Social Changes in Universities and Medical Schools for the Education of Future Physicians, *J Med Educ* 43:433, 1968.
 6. Wagner, R. R.: The Basic Medical Sciences, the Revolution in Biology, and the Future of Medical Education, *Yale J Biol Med* 35:1, 1962.
 7. Perkins, J. A.: *The University in Transition*, Princeton University Press, 1966.

Received for publication December 16, 1968

The Initiating Cause of Coronary Artery Thrombosis: an Anatomic Study

IRVING CHAPMAN, M.D.†

Since thrombi within the extramural branches of the coronary artery are superimposed on intimal erosions (1, 2, 3), and erosions of the intima are often seen without an overlying thrombus, it follows that the erosion precedes the thrombus; and as the raw collagen of the arterial wall, when directly exposed to blood, can clump platelets (4) and initiate a thrombus, it is apparent that the intimal erosion plays a key role in coronary artery thrombosis. This study was undertaken because of the limited available knowledge about the cause of the erosion.

Materials and Methods

Five segments of coronary artery containing thrombi superimposed on ulcerated atheromata, 6 segments with ulcerated atheromata without superimposed thrombi, and 8 segments with intact atheromata were examined. All 19 segments were fixed in 4 percent formaldehyde for 48 hours, decalcified for 24, divided longitudinally, and then processed through alcohol, xylol, and paraffin. Both halves were sectioned serially at 6 μ intervals along their longitudinal axis. Four of every 5 slides were stained in sequence by elastica Van Gieson, Gomoris' trichrome, Gomoris' reticulin, periodic acid Schiff, and phosphotungstic acid haematoxylin after Zenkerizing. A few slides were gram stained.

In this report, arteriosclerosis is used in a general sense to designate all of the changes which deform the coronary artery, and includes the foci of fibrosis and the deposits of calcium and lipid. Atheroma is used in the limited sense for intramural sites characterized by a localized collection of lipid rich, grumous material.

Findings

Although vasa vasorum were rarely seen within the intima and media of the unblemished coronary artery, there was a rich, easily visualized network in all coats of the arteriosclerotic segments. The largest branches of the vasa vasorum were in the adventitia; tributaries penetrated the media, at the intimal border divided into many branches which usually pursued a longitudinal course, and often anastomosed with other intimal branches (Figs. 2, 7, 8). Almost all of the vasa within the intima originated from, or emptied into adventitial arteries or veins. Occasionally, small arteries arose from the lumen

† Consultant in Pathology, Mount Sinai Hospital Services, City Hospital at Elmhurst, 79-01 Broadway, Elmhurst, N.Y. 11373.

Associate Clinical Professor, the Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

of a branch coronary artery and threaded their way laterally into the contiguous intima of the main artery; while in the rarest of instances, intimal vasa vasorum arose directly from the main coronary artery lumen. At times, the media of the coronary artery at the site of vasa vasorum penetration was partially or completely replaced by fibrous connective tissue, and some of the venous vasa which penetrated the media were dilated to sinusoidal proportions (Fig. 8).

There was a definite increase in vasa vasorum in the vicinity of all softened atheromata, whether intact or ulcerated. Many of these vasa were separated from the atheromatous cavity by a thin seam of intima which almost always showed degenerative changes, as evidenced by a diminution or absence of fibrocytes between lamellae of collagen which frequently stained with an altered eosinophilia (Figs. 2, 4, 7). Occasionally, in small focal areas of the intima, the collagen fibers showed a diminution of eosinophilia, and were separated by an increase in ground substance with a reduced density. These latter foci, which were suggestively the effect of acute edema, were always contiguous to intimal vasa vasorum. Infrequently, intimal vasa vasorum within, or close to an intact atheroma were ruptured with free blood present around their severed ends (Fig. 5). In one instance a fibrin thrombus was present within an adventitial branch of the vasa vasorum, and in another instance, within an intimal branch.

Inflammatory cell infiltrates, consisting of varying mixtures of lymphocytes, plasma cells, neutrophilic polymorphonuclears, and monocytes, and often accompanied by hemosiderin and lipin laden macrophages, usually circumscribed some segments of the vasa vasorum which coursed in the vicinity of softened atheromata (Figs. 2, 4, 5, 6, 8). Lymphocytes and plasma cells were more prominent around the intimal portion of these vasa, while the polymorphonuclear component was usually slightly more evident around the medial and adventitial sections. The hemosiderin laden macrophages were frequently seen within the intima at the site of medial penetration by the vasa vasorum; while the lipid laden macrophages, which at times were so numerous that they formed sheets of cells (Figs. 5, 6), were usually present within the intima near the base of the atheroma. These infiltrates varied in composition and intensity from one arteriosclerotic segment to the next, without any correlation with the size of the atheroma, presence of intimal ulceration, or superimposed thrombosis. The infiltrates were often scanty, and at times only present around small segments of the vasa vasorum; and in three specimens (two with eroded atheroma and one with an intact atheroma), they were absent.

Free fragments of detritus, which included calcified granular material, collagen fibers, lipid laden macrophages, acicular crystals, and clumps of eosinophilic amorphous material were shed into the atheromatous cavity from the seam of intima which circumscribed it (Figs. 1, 2, 3, 4, 7). The origin of these fragments was most obvious when they were distinctively marked by calcium, hemosiderin, or hematoidin; for they then could be easily envisioned conjoined to their site of intimal origin, which was similarly pigmented (Figs.

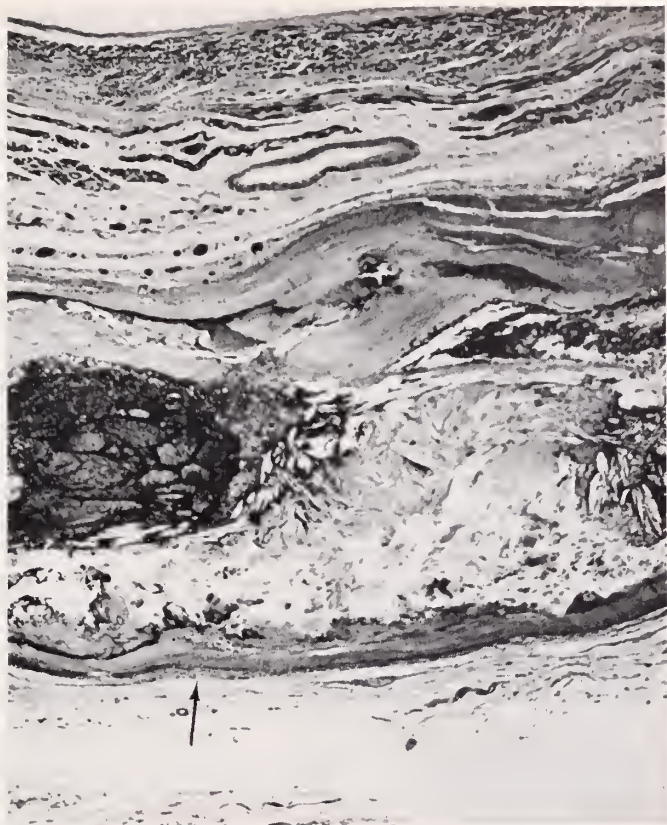


FIG. 1. Longitudinal section of coronary artery. A recent occluding thrombus, with atheromatous debris incorporated in its periphery, abuts on an eroded atheroma which obstructs the coronary artery lumen. Intimal fragments are shed from a large segment of the lower wall of the coronary artery. The fat contiguous to the upper wall is congested (magnification $\times 40$).

2, 4). In instances of atheromatous ulceration, the same free fragments of shed intima were often incorporated within a superimposed thrombus (Fig. 1).

Some of the arterial and venous vasa showed an unusual relationship which was similar to the plexiform and angiomatoid structures found in the lung in instances of chronic pulmonary hypertension (5) (Figs. 9, 10, 11). Although these angiomatoid structures were found in all coats of the coronary artery, they were seen most often in the intima and media. The simplest presentation was the indentation of the wall of a dilated thin walled venule by a small artery whose walls were in part composed of encircling layers of spindle shaped and rounded cells with clear cytoplasm (Fig. 9). In the most complex relationship, there were labyrinthine connections between small artery and vein, through a complicated sinusoidal network separated by baffles of tissue composed of spindle shaped and rounded cells, similar to those which composed the encircling coats of the small arteries (Figs. 10, 11).



FIG. 2. Area designated by arrow in Figure 1 shows shedding of intimal fragments, some of which are calcified, into atheromatous cavity. Distended vasa vasorum, with a few circumscribing lymphocytes, are separated from the atheromatous cavity by a thin seam of altered intima (magnification $\times 230$).



FIG. 3. Longitudinal section of coronary artery shows large intact atheroma which does not protrude into the lumen (magnification $\times 10$).

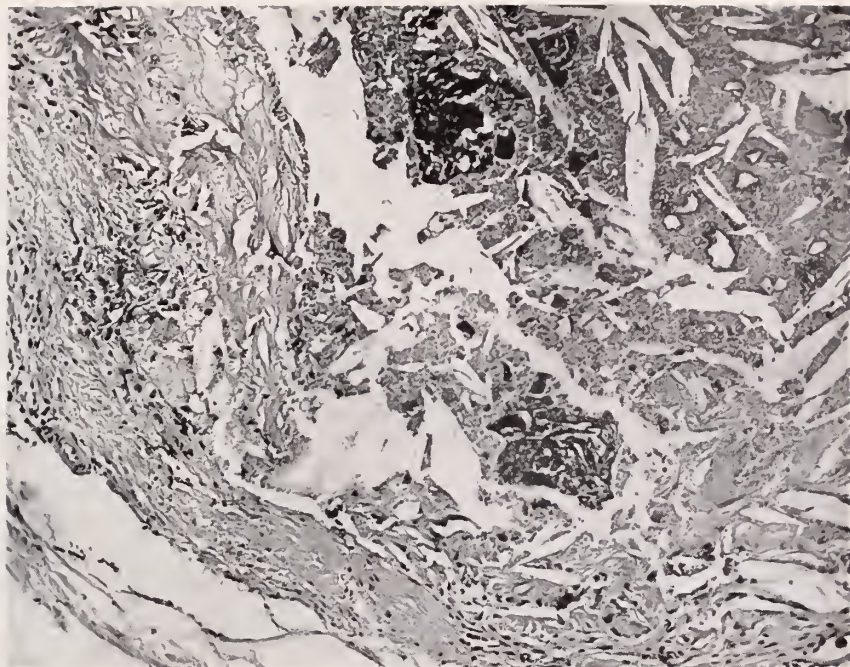


Fig. 4. Area designated by arrow in Figure 3 shows shedding of the intimal fragments from the thin seam of altered intima which rins the atheromatous cavity (magnification $\times 230$).

Intramural haemorrhages, both recent and remote, were found in many of the arterial segments. These haemorrhages could arbitrarily be separated into two groups. One would include haemorrhages which were usually larger, more often present in the superficial intima, almost always in direct continuity with the coronary artery lumen, and infrequently seen when the intima was apparently intact. The other group included smaller haemorrhages which were more often found in the deeper layers of the intima, and not connected with the lumen (Fig. 5). These were the predominant type found in intact vessels, although they were also seen at sites of ulceration, often in association with the larger, more superficial haemorrhages.

Moderate to severe venous congestion was frequently present within the pericardial fat immediately circumscribing a coronary artery segment which showed an intimal erosion (Fig. 1).

All of the anatomic changes in the coronary artery associated with softened, but intact atheromata, were essentially similar to those found with ulcerated atheromata, with or without superimposed thrombi; although the changes in the intact vessel were usually less severe (Figs. 1, 5).

Discussion

The observations from the present study were fashioned into a sequential description of the morphogenesis of the erosion of the coronary artery intima;

and an hypothesis was constructed to afford a reasonable depiction of the causal event relationships.

The most impressive finding was the intimate association of the vasa vasorum with each atheroma, whether intact or ulcerated, and the constancy of this anatomic pattern suggested a causal relationship. It was reasonable to assume that under usual conditions the vasa vasorum transuded a plasma ultrafiltrate, which was in turn absorbed by the venous and lymphatic vasa. The production and absorption of the ultrafiltrate would depend on the hemodynamic, colloidal, osmotic, and tissue pressures within and without the vasa vasorum, while their endothelial permeability would be an additional variable. Before estimating the net balance between these contending forces, it would be necessary to appreciate the singular anatomic distribution of the vasa within the sclerotic segments of coronary arteries. Almost all of the intimal vasa are branches of a relatively few vessels which penetrate the media; hence any embarrassment of the potentially vulnerable, transmedial circulation would affect large segments of the intima. If the arterial vasa within the media were totally obstructed, there could be ischaemic changes in the deeper portions of the subtended intima; while if the transmedial venous vasa should undergo a complete halt in flow with maintenance of some

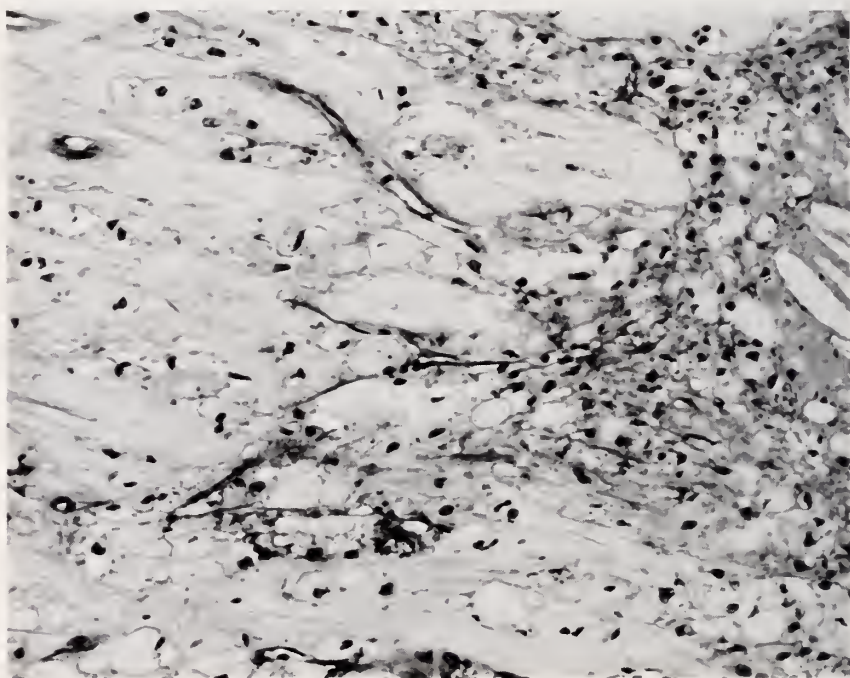


FIG. 5. Longitudinal section of coronary artery with intact atheroma. Two intimal capillaries are ruptured, and the blood which issues from their severed ends is mixed with atheromatous debris. The intact segments of the capillaries are circumscribed by lipid laden macrophages (magnification $\times 540$).

circulation in the arterial vasa, there would be congestion of the intimal venous vasa and an increased transudate within the intima.

It is reasonable to assume that some of the increased transudate exuding from the congested vasa which closely circumscribed the atheroma (Figs. 2, 4, 7) would suffuse into the atheromatous cavity, and that the current of suffusion might sweep into the atheroma fragments of intima which margined the cavity, and which were devitalized by previous occlusions of the nutritive arterial vasa. The addition of transudate and shed intimal fragments to the intact atheroma could increase the pressure on the retaining cap of intima, and contribute to its erosion. The rupture of this cap would radically alter the effect of the hemodynamic forces acting on the atheroma. Ordinarily, the column of blood within the coronary artery lumen acts like an internal tampon, compressing the atheroma. If the intimal roof of the atheroma was ruptured, however, the lateral pressure of the same column of blood within the coronary artery lumen would force the atheromatous debris through the intimal break, and in some instances the pressure of the extruded atheromatous debris could push a leaf of the disrupted intimal cap before it, so that it would project into the lumen in a baffle-like fashion (1).

The reasonableness of this hypothesis was now evaluated by determining its correspondence to anatomic findings, physiologic principles, clinical experience, and reason.

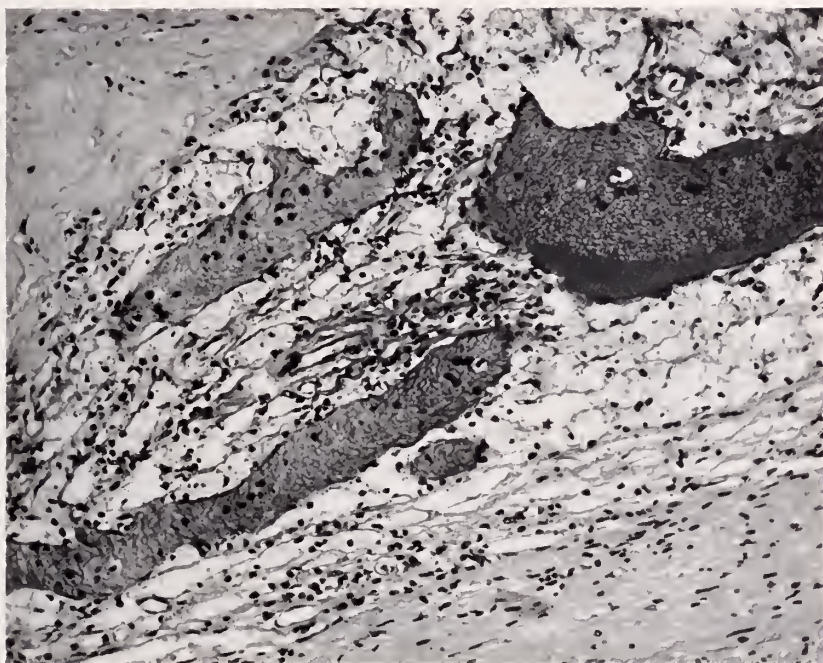


FIG. 6. Distended intimal vasa vasorum are circumscribed by sheets of lipid laden macrophages, as well as a slight, primarily mononuclear cell infiltrate (magnification $\times 230$).



FIG. 7. Longitudinal section of coronary artery. The upper layer of the intima shows a marked reduction in fibrocytes, as well as a diminished eosinophilia of the collagen. Fragments from this altered intimal layer are shed into the atheromatous cavity. Moderately congested vasa pursue a primarily longitudinal course within the deeper intimal layers (magnification $\times 120$).

All of the anatomic observations were consistent with the hypothesis, and none contradicted it. The key anatomic finding was the shedding of the intimal fragments into the intact atheromatous cavity. These fragments are dislodged by some force with a vector proceeding from within the wall of the coronary artery toward the lumen (1, 3). This vector could be due to a "pulling" force from the lumen or a "pushing" force originating in the wall. The only possible source of a "pulling" force from the coronary artery lumen is a Bernoulli effect, resulting from a rapid flow of blood through a narrow segment of lumen with a resultant reduction of lateral pressure. Since the majority of the intact, softened atheromata in this study did not narrow the lumen, and as these relatively flat atheromata contained shed intimal fragments similar to those with atheromata which protruded into the lumen (Figs. 1, 2, 3, 4), it is apparent that the Bernoulli effect could not be the prime cause for the shedding of the intimal fragments, but at the most could only be a contributory factor. By exclusion, therefore, we must search for some "pushing" force originating within the wall of the coronary artery. Since almost all of the tissue fragments shed into the atheroma originated from the thin seam of apparently altered intima interposed between the edge of the atheroma and the juxtaposed vasa vasorum (Figs. 2, 4, 7), it would be reasonable to suspect these vessels as the source of the disrupting force, and to indict the pressure of a brisk transudate exuding from these

vasa as the force itself. This assumption is supported by the following anatomic evidence: (1) The presence of hemosiderin pigment in the immediate vicinity of the intimal vasa, frequently at the site of penetration through the media. This could result from severe stasis of the venous vasa, resulting from compression of the transmedial branches. (2) The lipid laden macrophages surrounding some of the intimal vasa could result from the suffusion of lipoproteins through the wall of the congested venous vasa vasorum. It would be self evident that the qualitative and quantitative composition of these lipoproteins would reflect their quotient within the blood. (3) The sinusoidal dilatation of some venous vasa as they penetrated the media could be a reflection of severe congestion. (4) Foci characterized by an increase in ground substance, a separation of fibers, and a diminution of eosinophilia have been considered a result of edema. In the present series, such foci were always contiguous to vasa vasorum and could result from increased congestion of the venous vasa. (5) The finding of intimal petechia within coronary arteries with intact endothelium, can also be used to support the assumption that the congestion of the venous vasa vasorum can reach considerable levels. Generally, petechia are due to either small vessel disease, coagulation defects, inordinate and sustained increase in capillary pressure, or some combination of these three. Since coronary artery intimal haemorrhages are not notably increased in individuals who die with generalized petechiosis due to coagulation defects or generalized vascular disease, it is reasonable to assume, by exclusion, that the probable cause of intimal haemorrhages in intact coronary arteries is severe congestion of the vasa vasorum, and that all other factors may be contributory. (6) The finding of plexiform and angiomatoid bodies within the wall of the sclerotic coronary artery is additional corroborative evidence. Similar bodies are seen in the lung in some instances of long standing pulmonary hypertension, and some role in the regulation of blood flow is attributed to them (6). It is therefore possible that these plexiform and angiomatoid structures within the sclerotic segments of coronary artery indicate unduly raised pressures within portions of the vasa vasorum network. (7) The notable venous congestion in the pericardial fat which circumscribes sections of coronary artery containing recently eroded atheroma (with or without a superimposed thrombus), suggests that the segment of coronary artery, as well as its immediately surrounding tissues, may be affected by venous congestion at the time of intimal erosion.

Although these seven points of evidence are purely circumstantial, they can all be used to support the assumption that a force could be generated within the wall of the sclerotic coronary artery which could cause devitalized intimal fragments to be shed into the atheromatous cavity. Furthermore, there was no anatomic evidence, direct or circumstantial, to contradict this assumption.

Can the proposed hypothesis explain the genesis of intimal ulcerations which may encircle the entire circumference of the coronary artery, extend 2-3 cm in length, and appear preferentially in certain sites? Because of the

rich anastomosis of the vasa vasorum, a focal obstruction of an individual intramural vessel could not be an adequate cause. A conceivable mechanism could be a contracture of the media of sufficient magnitude to compress the vasa within large stretches of the media and to compromise the circulation to the extensive subtended intima. There is no anatomical or experimental evidence to support this speculation; and even if the spasm of the artery was a causative factor, it could not explain the prevalence of intimal erosion at selected sites of the extramural coronary arteries.

Recently Boucek (7) and his group have observed a most unusual movement of the coronary arteries during the cardiac cycle. Using cineangiography techniques, they demonstrated "areas of accentuated motion in the coronary arteries of man and the canine which are characterized by angulation and tortuosities of the coronary arteries during phases of the cardiac cycle. The left anterior descending artery becomes severely angulated during diastole, and the left circumflex and right coronary arteries during systole." Boucek's study shows that the right coronary artery undergoes angulation 2-3 cm from the ostium, as well as at the genu where the posterior descending artery begins; that the left anterior descending artery angulates most at the sites of perforating branches, while the left circumflex angulates most notably

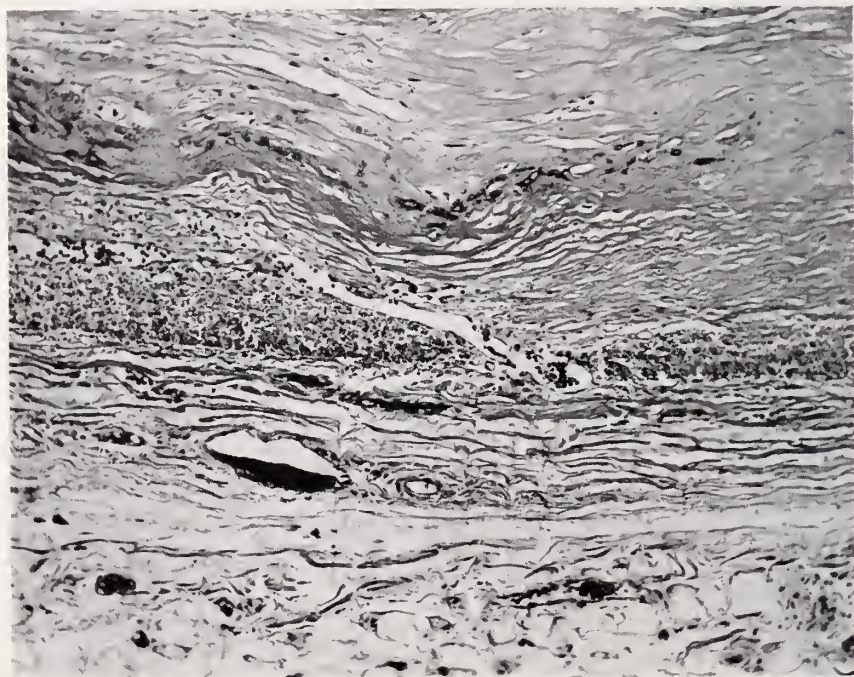


FIG. 8. Longitudinal section of coronary artery. Vasa which pursue a longitudinal course within the intima penetrate the media at a site which shows partial replacement of the muscle by fibrous connective tissue. The penetrating vein is dilated to sinuosoidal proportions. A slight, primarily mononuclear infiltrate accompanies portions of the intimal vasa (magnification $\times 120$).

within 1 cm of the ostium and at the origin of the marginal branch. Could these angulations contribute to the inordinate congestion of the venous vasa within the wall of the sclerotic coronary artery? There is supporting circumstantial evidence. In the first place, the angulations occur preferentially at the usual sites of intimal erosion and thrombosis. Secondly, the angulations cannot affect the intramural branches of the coronary artery which are tunneled into the myocardium, and ulcerated atheromata as well as thrombi are infrequently seen in the intramural branches of the coronary artery. Thirdly, the angulations would be a reasonable explanation for the association of coronary artery thrombosis with physical or mental stress with its associated increase in cardiac activity. Although this suggested role of the angulation has the advantage of simplicity, reasonableness, and some supporting circumstantial evidence, it is purely speculative. There are other possibilities. Neurohormonal effects on the vasa vasorum, as well as the singular characteristics of the coronary artery circulation during ventricular systole,

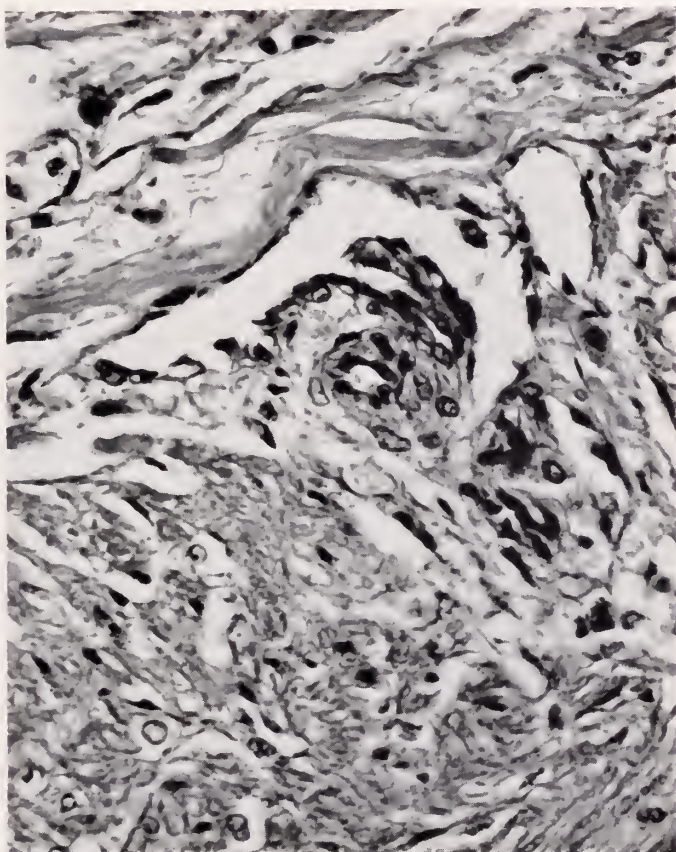
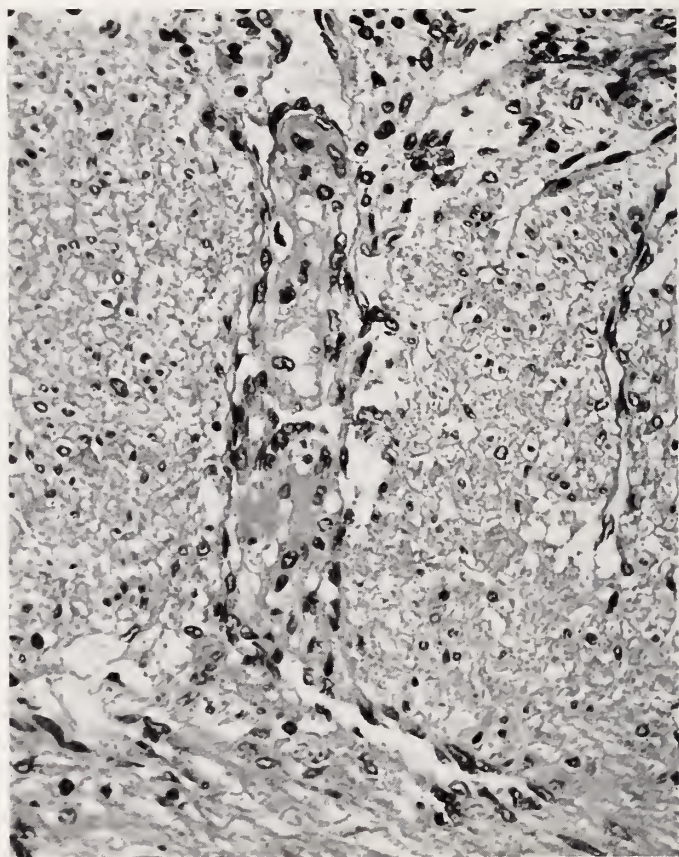


FIG. 9. Longitudinal section of coronary artery. A simple angiomatoid body in intima. An arteriole, with wall in part composed of plump cells with vesicular nuclei and vacuolated cytoplasm, juts into the distended capillary. Other slides from this set of serial sections show connection between arterial and venous circulation (magnification $\times 510$).

could cause significant changes in pressure within the vasa vasorum. These are subjects for physiological investigation.

Can any significance be attributed to the linear inflammatory infiltrate which often sheaths portions of the vasa vasorum in the vicinity of the softened or ulcerated atheroma? These infiltrates are probably the reaction to alterations within the atheroma. In some instances, however, the infiltrates may result from an infective agent which could increase the permeability of the vasa vasorum. Although the few gram stains done in this study did not demonstrate any bacteria within the wall of the coronary artery, the clinical experience of coronary artery thrombosis occurring during an inflammatory disease suggests that an infective mechanism may occasionally be a contributing factor.

The suggested morphogenesis of the erosion can also be utilized to explain the genesis of intramural haemorrhages within coronary arteries. The large, relatively superficial haemorrhages which are seen in instances of eroded in-



FIGS. 10 AND 11. Two representative angiomatoid bodies within the media. Baffles of tissue, composed primarily of cells which are suggestively similar to those which encircle the arteriole in Figure 9, separate the arterial and venous circulation (magnification $\times 540$).

tima, could arise from a back seepage of blood from the coronary artery lumen into an area of intimal entrapment; while the smaller, deeper haemorrhages could represent the escape of red blood cells from severely congested vasa, or from those which are ruptured when the intima is torn, because of the increase in subendothelial pressure by the increased exudate and shed intimal fragments.

It is probable that the addition of shed intimal fragments to the atheromatous cavity occurs in exacerbations and is cumulative, and that the softened atheroma develops over many years; while the erosion of the retaining cap is episodic with a definite end point.

The present description of the morphogenesis of an intimal erosion supplies a reasonable anatomic substrate for the clinical observation of undue physical or emotional strain preceding some cases of myocardial infarction.

We have not found previously recorded anatomic evidence to support the oft-voiced suspicion that the vasa vasorum are in some way causally related to coronary artery thrombosis (8, 9, 10, 11).

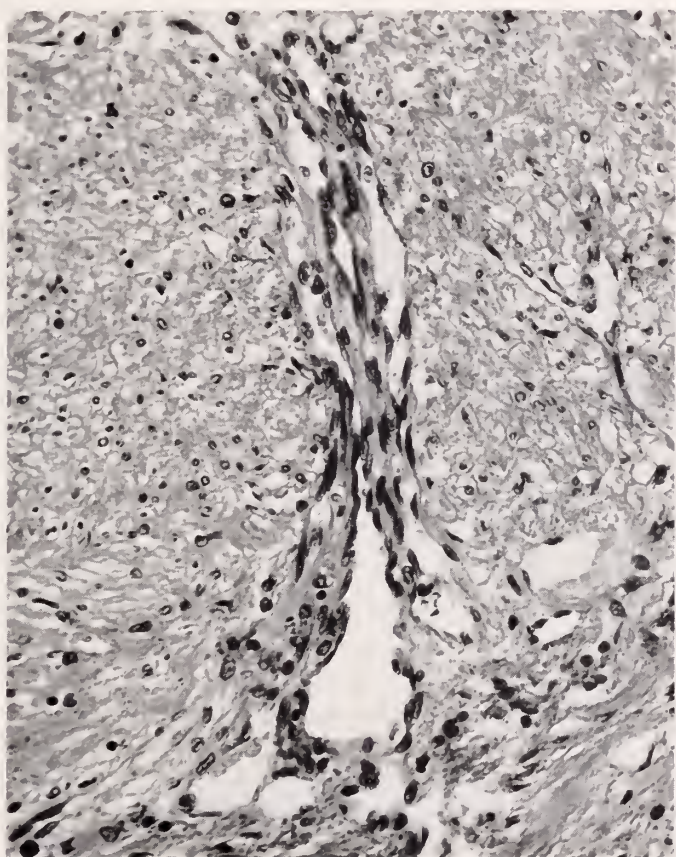


FIG. 11

Of the various anatomic alterations described in this report, attention may be called to three new observations. Plexiform and angiomatoid bodies had not been previously described within the wall of the coronary artery; there is no available description of the shedding of intimal fragments into the atheromatous cavity; and there is no available recorded appreciation of the relative sparsity and ease of compression of the transmural branches.

Summary

An intimal erosion precedes, and can initiate a coronary artery thrombus. Despite its obvious importance, detailed studies of the erosion's morphogenesis have been lacking. The present study indicates that the vasa vasorum, which are closely applied to every atheroma, produce an ultrafiltrate which under certain conditions can accumulate within the intima. The increased ultrafiltrate also cause fragments of devitalized intima to be shed into the intact atheromatous cavity, producing an erosive pressure on the overlying cap of intima.

Mechanisms are described which could cause devitalization of portions of the intima as well as an inordinate increase of ultrafiltrate.

Three of the anatomic observations made in this study had either not been previously described, or appreciated.

The proposed morphogenesis of an intimal erosion presents a reasonable anatomic substrate for the frequent clinical observation of an episodic onset of myocardial infarction preceded by physical or emotional stress.

References

1. Chapman, I.: Morphogenesis of Occluding Coronary Artery Thrombosis, *Arch Path* 80:256-261, 1965.
2. Constantinides, P.: Plaque Fissures in Human Coronary Thrombosis, *J Atheroscler Res* 6:1-17, 1966.
3. Friedman, M., and Van Der Bovenkamp, G.: The Pathogenesis of a Coronary Thrombus, *Amer J Path* 48:19-31, 1966.
4. Spaet, T. H., and Zucker, M. B.: Mechanism of Platelet Plug Formation and Role of Adenosine Diphosphate, *Amer J Physiol* 206:1267-1274, 1964.
5. Wagenvoort, C. A., Heath, D., and Edwards, J. E.: *The Pathology of the Pulmonary Vasculature*, Charles C. Thomas, Springfield 1964.
6. Mark, W.: Über Arterio-Venose Anastomosen, Gefäßssperren und Gefäße mit epitheloiden Zellen beim Menschen, *Z für Mikr Anat Forsch* 502:392-445, 1941.
7. Boucek, R. J.: Regional Coronary Artery Motion and Vascular Disease in *Biological Aspects of Occlusive Vascular Disease*, Ed. by D. G. Chalmers, and G. A. Gresham, Cambridge Univ. Press, 1964, p 136-155.
8. Paterson, J. C.: Capillary Rupture with Intimal Haemorrhage as a Causative Factor in Coronary Thrombosis, *Arch Path* 35:474-487, 1938.
9. Saphir, O., et al: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, *Amer Heart J* 10:762-792, 1934.
10. Koch, W., and Kong, L. C.: Über die Formen des Coronarverschlusses, die Änderungen in Coronar Kreislauf und die Beziehungen zur Angina Pectoris, *Beitr Path Anat* 90:21-84, 1932-33.
11. Winternitz, M. C., Thomas, R. M., and LeCompte, P.: *The Biology of Arteriosclerosis*, Charles C. Thomas, Springfield 1938.

Received for publication January 30, 1969

Disseminated Infection by *Mycobacterium Fortuitum*

KALMEN ALEX FEINBERG, M.D.†, AND S. STANLEY SCHNEIERSON, M.D.‡

Mycobacterium fortuitum, an acid fast bacillus, was first described as pathogenic for man by Cruz (1). Subsequently, the organism was classified as a Runyon Group IV, atypical acid fast bacillus (2).

Occasional instances of chronic pulmonary disease, cervical lymphadenitis, corneal ulceration, and subcutaneous abscesses have been attributed to *Mycobacterium fortuitum* (3, 4, 5, 6). Disseminated infection has not been reported. A case will be described in which disseminated infection with *Mycobacterium fortuitum* presented pathological features indistinguishable from the lesions of *Mycobacterium tuberculosis*.

Case Report

A 71-year-old Caucasian female was apparently well until six weeks prior to her hospitalization, when daily temperature elevations to 101°F and to 103°F were noted, with progressive weakness, weight loss, and malaise. She had no past history of tuberculosis.

On admission, she was alert, and her blood pressure was 140/80 mm Hg; pulse rate 84/min; respiratory rate 20/min; and temperature 98°F. Peripheral lymph nodes were not enlarged. The lungs were clear, and the examination of the heart revealed a regular sinus rhythm and an apical systolic murmur. A nontender liver was palpable one centimeter below the right costal margin, and the spleen and kidney were not felt. The neurological examination was within normal limits. Laboratory findings included a hemoglobin of 11.4 gm/100 ml, and white blood cell count of 9,200/cu mm, with a differential of 56% segmented neutrophils, 11% band neutrophils, 1% eosinophils, 22% lymphocytes, and 6% monocytes. The blood urea nitrogen was 14 mg, and the total protein 5.6 gm/100 ml, with an albumin of 2.7 gm and globulins of 2.9 gm.

On the third hospital day, the patient became stuporous. She responded to spoken voice by opening her eyelids and was able to follow simple commands. There was an increased tonus at the left elbow, and the left lower extremity fell much more rapidly from a flexed position than the right. Bilateral Babinski signs were present. When both upper extremities were raised in the air, the right fell faster than the left. The cerebrospinal fluid sugar was 52 mg, and protein 94 mg/100 ml. The sediment contained one white cell and two noneroded erythrocytes per cu mm. Cerebrospinal and blood cultures were negative. Electroencephalographic tracings were diffusely abnormal, and a right brachial angiogram was within normal limits. Chest

From the Departments of Pathology and Microbiology, The Mount Sinai Hospital, New York, N.Y. 10029.

† Resident, Department of Pathology, The Mount Sinai Hospital, New York, N.Y. 10029.

‡ Director of Microbiology, The Mount Sinai Hospital, New York, N.Y. 10029.

films revealed a scoliosis of the thoracic spine and lung fields free of infiltrations.

During the next five days a low grade fever appeared and she became less stuporous. Following a transient improvement, she developed severe headaches, hematemesis, and expired two days later.

Necropsy Findings

Numerous fine linear longitudinal ulcerations, with a red granular base, were found in the middle and lower third of the esophagus. The largest measured 6.0 cm in length and 0.5 cm in width (Fig. 1). A large, 5.0 × 3.0 cm, dark red submucosal hemorrhage was present in the upper third of the esophagus. The remainder of the esophageal mucosa revealed scattered small submucosal hemorrhages. In the distal half of the small intestine there were small, scattered, superficial mucosal erosions. The right lung weighed 400 gm and the left lung weighed 300 gm. They had apical pleural thickening. The upper lobes and right middle lobe were hypercrepitant, and the lower lobes slightly congested and hypoerepitant.

The paraesophageal lymph nodes at the level of the middle third of the esophagus were enlarged, soft, and matted together, the largest measuring 1.5 × 1.0 × 0.5 cm. These were adherent to the wall of the esophagus. On section, caseous necrosis was present. The lymph nodes at the pulmonary hilus were not enlarged, and disclosed only anthracotic pigment. The mesenteric lymph nodes were slightly enlarged, soft, and discrete.

A large, firm, nodular, well encapsulated, spherical mass projected from the ventral surface of the right tentorium cerebelli onto the subjacent right cerebellar hemisphere. It measured 5.0 × 4.0 × 3.5 cm, and was firmly attached to the surface of the tentorium. The underlying depression in the right cerebellar hemisphere measured 3.5 cm in maximum depth, and involved the medial one-third of the right hemisphere and the posterior half of the cerebellar vermis. The central portions of the fibromatous tumor were soft and yellow.

A large quantity of fresh blood was seen in the subarachnoid space of the

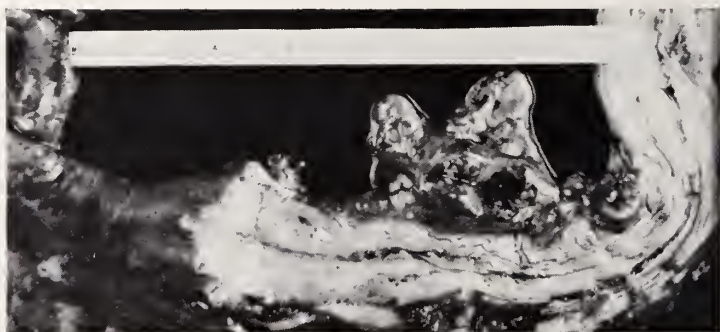


Fig. 1. Esophagus revealing fine linear ulcerations and matted caseous paraesophageal lymph nodes.

frontoparietal area. Transverse sections through the cerebrum showed an extensive fresh hemorrhage replacing most of the central white matter, and large segments of cortex throughout the left frontoparietal region. It measured 8.0 cm anteroposteriorly, 5.0 cm transversely, and 6.0 cm dorsoventrally, and had ruptured through the cortex of the left superior and middle frontal gyri into the subarachnoid space.

Microscopic Findings

The base of the esophageal ulcerations contained numerous caseating and noncaseating tubercles. Some of these were confluent. They involved the submucosa, muscularis, and extended into the adventitia (Fig. 2).

The paraesophageal lymph nodes were partially replaced by caseating giant cell granulomas containing acid fast bacilli.

Minute tubercles were present in the periportal and central portions of the hepatic lobules. One small caseous tubercle was found in the red pulp of the spleen, adjacent to a trabecular vein. Noncaseous tubercles were also seen in the lamina propria of the ileocecal valve and in a mesenteric lymph node. An extensive search of the lungs and hilar lymph nodes revealed no granulomas.

The intracranial mass was a benign meningioma with central necrosis. Multiple sections through the left superior, middle frontal, and cingulate gyri disclosed fresh hemorrhage, but no granulomas.

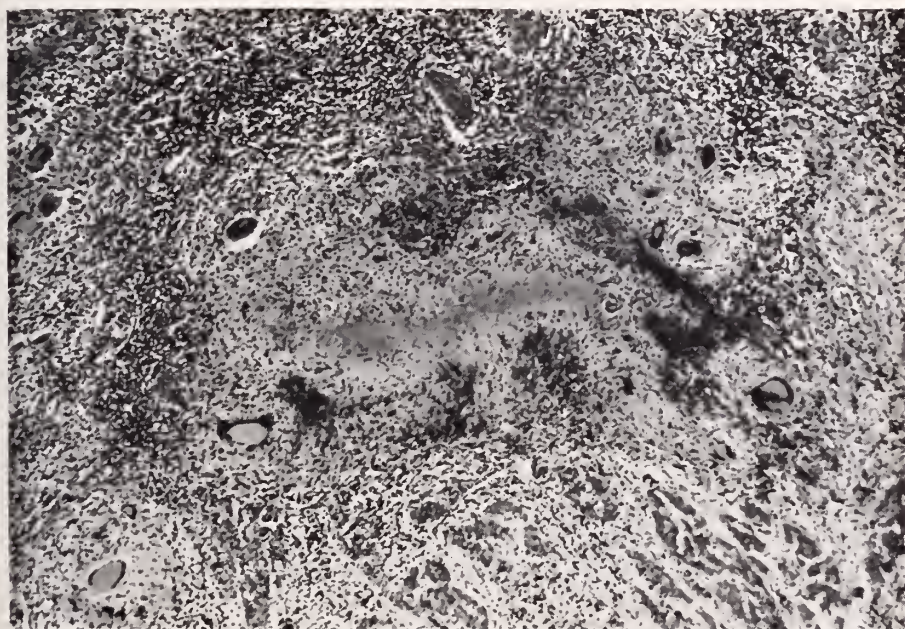


FIG. 2. Caseating giant cell tubercles in the submucosa and muscularis of the esophagus H-E ($\times 1000$).

Mycobacteriology

Identification of the acid fast strain, isolated in this case from a para-esophageal lymph node obtained at necropsy as *Mycobacterium fortuitum*, was based upon the following characteristics.

It was nonpigmented, and grew within three days on Lowenstein-Jensen medium. It grew in thioglycollate medium at 37°C and at 25°C. Niacin was not produced, and cord formation was absent. Strong catalase activity was noted at room temperature and at 68°C. The aryl sulfatase test was strongly positive. Finally, upon intraperitoneal injection, it was nonvirulent for guinea pigs and rabbits.

Discussion

In mycobacterial infections due to tuberculosis, primary esophageal lesions are virtually unknown. When they do occur, they are late manifestations of dissemination from pulmonary tuberculosis, or tuberculous thoracic spondylitis (7).

In this case report, a primary infection of the esophagus was due to a Group IV, rapid growing, acid fast bacillus, *Mycobacterium fortuitum*. The primary nature of the esophageal lesions is established because a thorough search of the lungs, tracheobronchial lymph nodes, and vertebrae did not reveal any granulomas.

The granulomatous ulcers in the esophagus, together with the lymphadenitis of the regional nodes, fulfill the criteria for a primary complex.

Early dissemination is documented by the miliary foci in the liver, spleen, and ileocecal valve.

Within recent years there has been an increased awareness of the importance played by the "atypical" mycobacteria in medicine. Although the majority of mycobacterial infections today are caused by *Mycobacterium tuberculosis*, the "atypical" mycobacteria are steadily gaining in incidence.

The various granulomatous infections in which acid fast bacilli are encountered does not classify the etiologic agent as *Mycobacterium tuberculosis*. Cultural characteristics and biochemical determinations are indispensable for proper identification of the various species. These methods are not just academic because these organisms respond differently to antituberculous chemotherapy. Also, the various groups differ widely in their response to drug susceptibility. *Mycobacterium fortuitum* is resistant to isoniazid and to p-aminosalicylic acid, but varies in its susceptibility to streptomycin.

It is therefore important that the mycobacteria are properly classified. Precise identification will expand our knowledge of the various increasing infections that these "atypical" mycobacteria cause in man, and will enable the physician to administer effective drug therapy.

Summary

A case of primary infection of the esophagus due to *Mycobacterium fortuitum*, with involvement of the regional lymph nodes and early visceral

dissemination is described. To our knowledge, this represents the first reported case of disseminated disease due to *Mycobacterium fortuitum*. The acid fast bacillus which was identified as *Mycobacterium fortuitum*, was isolated from a caseating paraesophageal lymph node. The importance of cultural and biochemical determinations are emphasized.

References

1. Cruz, J. C.: *Mycobacterium Fortuitum* un Bacilo Acido-Resistente Patogenico para o Homem. *Acta Med (Rio de J)* 1:297, 1938.
2. Runyon, E. H.: Anonymous *Mycobacteria* in Pulmonary Disease, *Med Clin N Amer* 43:273, 1959.
3. Corpe, R. F., Smith, C. E., and Steigus, I.: Death due to *Mycobacteria Fortuitum*, *JAMA* 177:262, 1961.
4. Wells, A. Q., Aguis, E., and Smith, N.: *Mycobacterium Fortuitum*, *Amer Rev Tuberc* 72:53, 1955.
5. Turner, L., and Stenson, B. S.: *Mycobacterium Fortuitum* as a Cause of Corneal Ulcer, *Amer J Ophthal* 60:329, 1965.
6. Beck, A.: *Mycobacterium Fortuitum* in Abscesses of Man, *J Clin Path* 18:307, 1965.
7. Bockus, H.: *Gastroenterology*, W. B. Sanders Co., Philadelphia, Pa. 1963, Vol I, p 210.

Received for publication December 11, 1968

Polymyxin B-Induced Respiratory Paralysis Reversed by Intravenous Calcium Chloride*

ROBERT AARON LEVINE, M.D.†

IN CONJUNCTION WITH

MICHAEL P. BEIBER, M.D., FRANCIS A. FORTE, M.D., STEVEN P. GERSTEN, M.D., MARK E. KRUGMAN, M.D., NORMAN ROSENSTOCK, M.D., HERBERT S. SHERRY, M.D., AND
GEORGE A. VIOLIN, M.D.

A total of 22 cases of respiratory paralysis associated with polymyxin B and colistimethate administration have been reported to date. A recent review by Lindesmith et al (1) appears in the literature.

The mechanism of the neuromuscular blockade induced by polymyxin B and its treatment are unknown. This report describes one additional case of respiratory paralysis induced by intravenous polymyxin B, and its prompt reversal by intravenous administration of calcium chloride. A finding in our case was the presence of abnormally low serum ionized calcium concentrations during the apneic period. In view of this observation, we have thought it worthwhile to review the possible mechanisms and management of neuromuscular blockade associated with polymyxin B, with general emphasis on the role of calcium.

Methods

Sodium and potassium were determined by flame photometry. Creatinine was determined employing an auto analyzer. Total calcium was determined by atomic absorption spectrophotometry. Ionized calcium was measured by a calcium activity electrode (Calcium Activity Electrode, Model 92-90, manufactured by Orion Research, Inc., Cambridge, Massachusetts) in accordance with the method outlined by Oreskes et al (2). The assays for polymyxin B were kindly performed by Dr. I. Levenstein (Lereo Labs, Roswell Park, New York) using the cylinder plate method, employing *Brucella bronchiseptica* as the assay organism.

Case Report

A 54-year-old white female was admitted to The Mount Sinai Hospital for the first time on December 12, 1967 because of pancytopenia. After evaluation, it was felt that the patient had aleukemic leukemia. She was managed supportively under careful observation.

From the Department of Internal Medicine, the Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

* This study was supported in part by a grant from Burroughs Wellcome & Co., Tuckahoe, New York.

† Requests for reprints should be addressed to Robert Aaron Levine, M.D., Department of Internal Medicine, the Mount Sinai School of Medicine of The City University of New York, 100th Street and Fifth Avenue, New York, N.Y. 10029.

The patient was well until one month following discharge, at which time she developed fever and a cough. Following three days of fever, she was readmitted on January 20, 1968. Blood pressure was 105/55 mm Hg; pulse 100 per minute and regular; respirations 20 per minute and regular; temperature 100°F; and weight 137 lbs. Examination of the abdomen revealed the liver edge to be palpable six fingerbreadths below the right costal margin, and the spleen palpable two fingerbreadths below the left costal margin. The hemoglobin was 7 gm/100 ml; WBC 7900/mm³ with 12% blasts; platelets 34,000/mm³; bone marrow aspirate 46% blasts. Blood concentrations of sodium, potassium, urea (BUN), creatinine, glucose, bicarbonate, chloride, SGOT, and SGPT were all within normal limits. Serum calcium and phosphorus were 9.7 mg/100 ml and 3.1 mg/100 ml respectively, both within normal limits. Total protein was 7.3 gm/100 ml, and albumin 3.3 gm/100 ml. The EKG showed nonspecific ST and T wave changes. The Q-T interval was normal. Shortly after admission the patient developed fever spiking to 104°F, with clinical signs of sepsis. No site of infection was identified. Following appropriate cultures, she was started on sodium cephalothin 2 gm intravenously every six hours, and kanamycin 250 mg intravenously every six hours, with no clinical improvement. After three days, colistimethate 50 mg intramuscularly every 12 hours was added. There was gradual improvement, and by the eleventh day of treatment the patient became afebrile. After four days without fever, all antibiotics were discontinued. Blood and platelet transfusions were given as needed. On February 13, she received one dose of daunomycin 95 mg intravenously. Two days later, the patient developed spiking fevers and clinical sepsis. After appropriate cultures were taken, she was started on methicillin 4 gm every 8 hours intravenously, chloramphenicol 1 gm every 6 hours intravenously, and polymyxin B 100 mg every 12 hours intravenously.

On February 17, 48 hours after initiating polymyxin B therapy, the fourth intravenous infusion of polymyxin B sulfate (Aerosporin®, Burroughs Wellcome & Co), 100 mg dissolved in 200 ml of normal saline, was begun. Ten minutes after the infusion was started the patient became agitated and progressively dyspneic. Two minutes later, the infusion was stopped after 85 mg of the drug had been administered. The patient was now unconscious, apneic, and unresponsive, with a barely palpable pulse (in the 24 hours prior to the respiratory arrest, the patient had received the following medication: polymyxin B 200 mg intravenously; chloramphenicol 4 gm intravenously; methicillin 12 gm intravenously; sodium penicillin 20 million units intravenously; and potassium penicillin 20 million units intravenously. Oral medications were isoniazid 300 mg; prednisone 15 mg; pyridoxine 50 mg; cyproheptadine 15 mg; dioctyl sodium sulfosuccinate 300 mg; glycerol guaiacolate 20 ml; and saturated solution of potassium iodide 40 drops. Urine output was adequate. The BUN was 27 mg/100 ml). Immediate respiratory resuscitation was begun, with endotracheal intubation and positive pressure ventilation. The cyanosis was relieved and the pulses became easily palpable.

The EKG at this time revealed sinus tachycardia, with nonspecific ST and T wave changes. The Q-T interval and S-T segment were significantly prolonged (Fig. 1). There were no seizures associated with the episode. Three minutes after resuscitation, the patient, although apneic and dependent upon mechanical ventilation, was able to move all extremities upon request. The patient remained alert and able to respond to all questions with gesticulations. She denied paresthesias prior to, or during this period. Chvostek and Trousseau signs were negative. Deep tendon reflexes were absent except for the left achilles reflex, which was normal. Plantar reflexes were flexor.

Beginning 1½ hours after the onset of apnea, and periodically thereafter, the patient's ventilatory function or maximum breathing capacity (MBC) was measured, employing a Wright respirometer (Ainci, Hudson, New York) attached to the patient's cuffed endotracheal tube. This was accomplished by disconnecting the patient from the positive pressure apparatus, waiting 5 seconds for the patient's thorax to reach equilibrium, and connecting the respirometer to the cuffed endotracheal tube for 15 second periods. Venous blood was obtained periodically for determination of electrolytes, polymyxin B levels, ionized calcium levels, and total calcium levels.

The respiratory arrest was unaffected by the administration of two doses of edrophonium (Fig. 2). One hour and 55 minutes after the onset of apnea, 10 ml of 10% calcium chloride was administered intravenously in a 2 minute period. A prompt increase, almost fivefold, was noted in the patient's maximum breathing capacity. This improvement in ventilatory function was maintained for about 1 hour, at which time the apnea recurred. The intravenous administration of 10 ml of 10% calcium chloride was repeated, and was promptly followed by improved ventilation. Subsequently, the patient was able to maintain respiration spontaneously until she expired. The patient received one liter of dextrose 5% in normal saline during the apneic period. She received no potassium.

At the onset of apnea, polymyxin B, sodium and potassium penicillin, and methicillin were immediately discontinued, and after recovery from the apnea, the patient was treated with intravenous cephalothin and chloramphenicol. However, the patient's clinical condition deteriorated, and she expired on February 19, 1968.

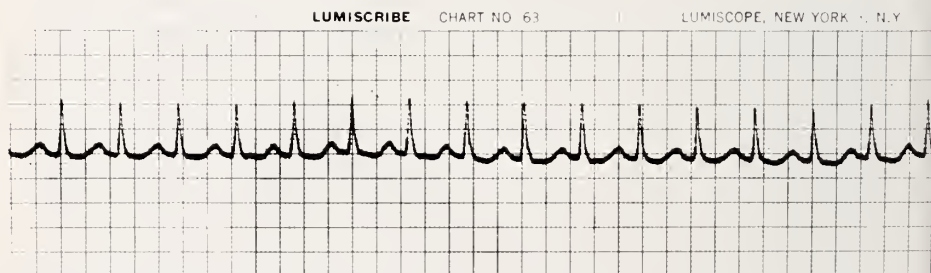


Fig. 1. Electrocardiogram taken one hour after onset of apnea. Note prolonged Q-T interval (lead V-5).

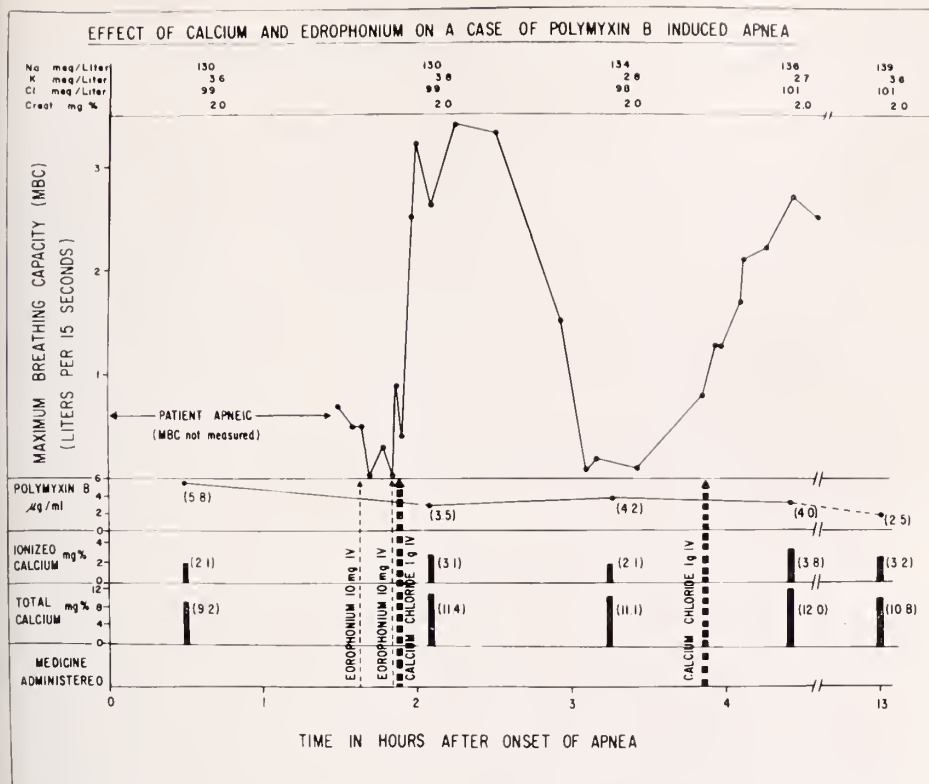


FIG. 2. A summary of the patient's clinical course and laboratory values beginning at onset of apnea, continuing for 13 hours.

Postmortem examination revealed morphological changes compatible with acute blastic leukemia in the bone marrow, liver, spleen, and lymph nodes. There was no evidence of central nervous system leukemia or bleeding, nor any central nervous system abnormality. The autopsy included careful sectioning of the brain stem. Focal pulmonary hemorrhages, interstitial pneumonitis, and bronchopneumonia were present. The kidneys showed signs of mild pyelonephritis.

Results

APNEIC PERIOD: FIGURE 2

As illustrated in figure 2, a prompt improvement in MBC followed the intravenous administration of 10 ml of 10% calcium chloride after 2 doses of edrophonium had proved ineffective. A sample of this patient's serum, withdrawn minutes after the onset of apnea, revealed the ionized calcium concentration to be 2.1 mg/100 ml. The serum total calcium concentration was 9.2 mg/100 ml. Ten minutes after one gram of calcium chloride was administered intravenously, the serum ionized calcium concentration increased to

3.1 mg/100 ml, and the serum total calcium concentration to 11.4 mg/100 ml. When the patient again became relatively apneic, the serum ionized calcium concentration fell to 2.1 mg/100 ml, with a total calcium concentration of 11.1 mg/100 ml. The serum ionized calcium concentration following the second injection of calcium chloride was 3.8 mg/100 ml, with a serum total calcium concentration of 12.0 mg/100 ml. At this time the patient was breathing well, without the aid of a respirator. Thirteen hours after the onset of apnea, the serum ionized calcium concentration was 3.2 mg/100 ml, with a serum total calcium concentration of 10.8 mg/100 ml. The serum concentration of potassium was normal prior to the onset of apnea and 30 minutes after the onset of apnea. The hypokalemia observed 3½ and 4½ hours after the onset of apnea was no longer present at 13 hours. The patient received no potassium during the apneic period. The serum creatinine of 2 mg/100 ml, indicating a mild renal insufficiency, remained constant throughout the apneic period. Measured serum concentrations of polymyxin B, the first measurement taken 30 minutes after the onset of apnea, were all within the usual therapeutic range.

Discussion

The acute onset of apnea, which was temporally associated with the intravenous administration of 85 mg of polymyxin B over 12 minutes (rate in excess of suggested rate of administration), strongly suggests an etiology of neuromuscular blockade as the cause of the apnea. Other medications that the patient received at the time, or 48 hours prior to the onset of apnea, have not been reported to induce apnea. The rare association of acute leukemia with apnea has been reported, but this has been on the basis of localized leukemic infiltrate, or hemorrhage in the central nervous system (3). The postmortem examination failed to reveal lesions within the central nervous system. Apnea in the absence of brain stem symptoms has not been reported as a result of leukemia alone.

Neuromuscular blockade, as evidenced by reversible respiratory paralysis, has been reported in 22 cases as a rare adverse reaction of polymyxin B or colistimethate (4-14). Restlessness and dyspnea preceded the onset of apnea. Several of the patients had other neurologic symptoms as well, including diplopia, dysarthria, ptosis, and lethargy. In all but 3 cases, the apnea lasted for less than 24 hours. In 18 of the 22 reported cases, the patients had underlying renal disease.

Only 1 case in the literature described calcium reversal of apnea due to colistimethate (13), a drug closely related to polymyxin B. In that case, a 49-year-old woman developed postoperative apnea. Calcium reversed the apnea, while edrophonium was not effective. The patient had received 17 doses of colistimethate prior to surgery. She had also received curare 30 mg during the surgery.

Although we have shown that calcium chloride was associated with reversing the apnea induced by polymyxin B in this patient, other authors have

found calcium to be ineffective in reversing polymyxin B or colistimethate induced neuromuscular blockade both *in vitro* (15, 16) and *in vivo* (5, 7).

The failure of edrophonium to reverse the polymyxin B-induced apnea observed in this study is in agreement with the results of others (5, 15, 17).

The patient herein reported experienced improvement in ventilation following the intravenous administration of calcium chloride. This observation, along with the findings of abnormally low serum ionized calcium concentrations, suggests the following possible mechanisms by which calcium may induce improvement in polymyxin B-induced apnea:

- (1) Correction of a hypocalcemic state induced by polymyxin B.
- (2) The amelioration of a relative calcium deficiency at the neuromuscular junction due to (1) or due directly to the presence of polymyxin B at, or near the neuromuscular junction.
- (3) A pharmacologic activity of the calcium acting upon the neuromuscular junction, counteracting the neuromuscular blockade induced by polymyxin B.
- (4) Direct antidotal activity of calcium upon the polymyxin B molecule rendering it nontoxic to the neuromuscular junction.

The first explanation is supported by the low serum ionized calcium concentration observed during the apneic period, and by the prolonged Q-T interval in the EKG taken during the apneic period while the patient was assisted by the respirator. The possibility exists, however, that the prolonged Q-T interval was the result of respiratory alkalosis induced by mechanical over ventilation (unfortunately blood gases were not obtained acutely). However, hypocalcemia alone does not result in respiratory paralysis, except consequent to laryngospasm. Similarly, EDTA has not been reported to induce neuromuscular blockade resulting in apnea. In addition, the patient showed no signs of hypocalcemia tetany.

In vitro determinations of serum ionized calcium concentrations, employing a calcium activity electrode in the presence of pharmacologic amounts of polymyxin B, appear to reveal a lowering of serum ionized calcium concentration by polymyxin B. Studies concerning the chemical nature of this observation and its significance are in progress by the author and an associate.

The second, third, and fourth explanations remain as distinct possibilities. Polymyxin B is thought to act as a surface active agent. It has both lipophobic and lipophilic groups. These are thought to produce disorientation of the lipoprotein lamellae of the bacterial cell, with resulting permeability changes which allow the cell contents to escape (18). Polymyxin B has been shown to be bound in the area of the cell membrane. It has further been shown that those molecules which inhibit the binding of polymyxin B to the cell wall of the bacteria, do so in proportion to their affinity for the phosphate group (18). Calcium has been shown to antagonize the antibacterial effect of polymyxin B *in vitro*. This is thought to occur by competition with polymyxin B for the cellular binding sites. It occurs with the administration of physiological amounts of calcium. Polymyxin B and calcium may compete for central sites at

the neuromuscular junction, similar to polymyxin's competition with polyvalent cations, including calcium, for anionic binding sites on the pseudomonas cell membrane (18). Both gram-negative bacteria and neurons are rich in phospholipids. The reported increased sensitivity of patients with chronic renal disease to the neuromuscular blockade induced by polymyxin B (1) may be due in part to the low serum calcium levels found in some azotemic patients.

Summary

Acute respiratory paralysis is a rare, but usually reversible complication of polymyxin B and colistimethate therapy. The present case report is the first one in which the two apneic periods were documented to be associated with abnormally low serum ionized calcium concentrations. The possible therapeutic value of intravenous calcium chloride in reversing the polymyxin B-induced respiratory paralysis is discussed.

Acknowledgments

The authors are indebted to Dr. Sherman Kupfer, Miss Portia Cutchin, and Mrs. Noami Buchholz for both advice, and for the performance of the serum ionized calcium concentration determinations in the facilities of the Clinical Research Center of The Mount Sinai Hospital, New York, N. Y. 10029 (supported by the National Institutes of Health, Grant FR-751).

Generic and Trade Names of Drugs

Polymyxin B—*Aerosporin*
Colistimethate—*Coly-mycin M Injectable*
Cephalothin—*Keflin*
Kanamycin—*Kantrex*
Methicillin—*Staphcillin*
Chloramphenicol—*Chloromycetin*
Cyproheptadine—*Periactin*
Dioctyl sodium sulfosuccinate—*Colace*
Edrophonium—*Tensilon*
Isoniazide—*Seromycin*
Prednisone—*Deltasone*
Pyridoxine
Glycerol guaiacolate
Daunomycin

References

1. Lindesmith, L. A., Baines, R. D., Biglow, D. B., and Petty, T. L.: Reversible Respiratory Paralysis Associated with Polymyxin Therapy, *Ann Intern Med* 68:318-327, 1968.
2. Oreskes, I., Hirsch, C., Douglas, K. S., and Kupfer, S.: Measurement of Ionized Calcium in Human Plasma with a Calcium Selective Electrode, *Clin Chim Acta* 21:303-313, 1968.
3. Williams, H. M., Diamond, H. D., and Craver, L. F.: The Pathogenesis and Manage-

ment of Neurological Complications in Patients with Malignant Lymphomas and Leukemia, *Cancer* 11:76-82, 1958.

4. Bush, G. H.: Antibiotic Paralysis, *Brit Med J* 2:1062-1063, 1962.
5. Small, G. A.: Report of a Case: Respiratory Paralysis after a Large Dose of Intraperitoneal Polymyxin B and Bacitracin, *Anesth Analg* 43:137-139, 1964.
6. Barlow, M. B., and Groesbeck, A.: Apparent Potentiation of Neuromuscular Block by Antibiotics, *S Afr Med J* 10:135-136, 1966.
7. Pohlmann, G.: Respiratory Arrest Associated with Intravenous Administration of Polymyxin B Sulfate, *JAMA* 196:181-183, 1966.
8. Fekety, R. R. Jr., Norman, P. S., and Cluff, L. E.: Treatment of Gram-negative Bacillary Infections with Colistin: The Toxicity and Efficacy of Large Doses in Forty-Eight Patients, *Ann Intern Med* 57:214-229, 1962.
9. Perkins, R. L.: Apnea with Intramuscular Colistin Therapy, *JAMA* 190:421-424, 1964.
10. Rapin, M., Bagros, P., Amiel, C., Barois, A., and Coulon, M.: Acute Interstitial Nephropathy and Neurologic Disorders during a Massive and Prolonged Treatment with Colistin Methanesulfonate, *Presse Med* 73:1529-1534, 1965.
11. Parisi, A. F., and Kaplan, M. H.: Apnea during Treatment with Sodium Colistimethate, *JAMA* 191:298-299, 1965.
12. Anthony, M. A., and Louis, D. L.: Apnea due to Intramuscular Colistin Therapy: Report of a Case, *Ohio Med J* 62:336-338, 1966.
13. Zauder, H. L., Barton, N., and Bennett, E. J.: Colistimethate as a Cause of Postoperative Apnea, *Canad Anaesth Soc J* 13:607-610, 1966.
14. McQuillen, M. P., Cantor, H. E., and O'Rourke, J. R.: Myasthenic Syndrome Associated with Antibiotics, *Arch Neurol* 18:402-415, 1968.
15. Adamson, R. H., Marshall, F. N., and Long, J. P.: Neuromuscular Blocking Properties of Various Polypeptide Antibiotics, *Proc Soc Exp Biol Med* 105:494-497, 1960.
16. Naiman, J. G., and Martin, J. D.: Some Aspects of Neuromuscular Blockade by Polymyxin B, *J Surg Res* 7:199-206, 1967.
17. Timmerman, J. C., Long, J. P., and Pittinger, C. B.: Neuromuscular Blocking Properties of Various Antibiotic Agents, *Toxic Appl Pharmacol* 1:299-304, 1959.
18. Newton, B. A.: Site of Action of Polymyxin on *Pseudomonas Aeruginosa*: Antagonism by Cations, *J Gen Microbiol* 10:491-499, 1954.

Received for publication February 5, 1969

Pancreatic Disease: A Review

DAVID A. DREILING, M.D.†

Pancreatic Inflammation

It is convenient to consider pancreatitis as the sum of the inflammatory changes occurring within the pancreas, a spectrum which includes the dramatic eruption of acute hemorrhagic necrosis of acute pancreatitis at one end, and the protracted debilitating metabolic consequences of chronic pancreatitis at the other end. The convenience of this assumption is probably an oversimplification of the fact that what we call "pancreatitis" is the manifestation of a wide variety of disorders.

This section is concerned with the clinical recognition and therapeutic management of inflammatory disorders of the pancreas. It assumes that a rational approach to this group of still-puzzling problems depends on sorting out the various kinds of pancreatitis.

ACUTE PANCREATITIS

1. Definition. Acute pancreatitis is an acute inflammation of the pancreas, and may be defined as a chemical autolytic disorder with escape of activated proteolytic and lipolytic enzymes into the gland. The process is considered to be one of localized autodigestion and tissue disruption.

2. Etiologies. It is generally held that there is no single etiology for acute pancreatitis. The association with biliary tract disease and alcoholism is well known, as well as the precipitation of an episode of acute pancreatitis by a big meal. Table I lists factors believed to be operative in clinical forms of pancreatitis and their corresponding experimental forms. Reflux of bile into the pancreatic ducts (the common channel theory), probably the oldest hypothesis, has not enjoyed as much support in recent years as has the concept of hypersecretion of the pancreas against ductal obstruction with resultant glandular disruption. The association of pancreatitis with such metabolic situations as essential hyperlipemia, hyperparathyroidism, and the postpartum state should be remembered.

3. Clinical Features. Acute pancreatitis varies greatly in the intensity of its clinical manifestations. It occurs in almost all age groups, although predominantly in middle life, and almost equally in both sexes. Those instances associated with biliary tract disease perhaps occur more in women, while the forms associated with alcoholism occur more in men. The onset is acute, with severe abdominal pain, often following a large meal or indiscretion in alcoholic intake. The pain extends across the epigastrium from right to left and frequently to the back. Marked nausea and vomiting often occur, with cessation of intestinal activity. Chills are rare, but fever is present in all patients and often reaches

† Professor of Surgery, the Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

TABLE I

Etiologic Factors in Pancreatitis and the Corresponding Clinical and Experimental Varieties

Etiologic Factor	Clinical Variety	Experimental Variety
Infectious	Mumps ?Choleecystic disease	Coxsackie virus
Mechanical	Acute hemorrhagic, edematous and necrotic pancreatitis	Ductal ligation; secretory stimulation
Common channel Obstruction-hypersecretion	Chronic pancreatitis Cholecystic disease Choledocholithiasis ?Alcoholism Hydatid, Clonorchis and Ascaris infestation	Ductal injection
Metabolic-nutritional	Essential hyperlipemia Hemachromatosis, siderosis Kwashiorkor and protein deficiencies Alcoholism, cirrhosis, Sprue, ulcerative colitis, diffuse jejunoileitis Hyperparathyroidism ?Pregnancy	Ethionine Protein-deficient feeding
Vascular	Diabetic ketosis Terminal pancreatitis (arterio-sclerosis, coronary) Periarteritis, lupus erythematosus	Vascular insufficiency
Toxic	Methyl alcohol poisoning	Zinc poisoning Alloxan Cobaltous chloride poisoning
Allergic	Periarteritis nodosa	Arthus and Schwartzman phenomena
Traumatic	External trauma Operative trauma	Incisional Ductal transection

high levels. Evidences of shock are readily apparent, i.e., hypotension, tachycardia, and cyanosis of the nail beds and lips.

The abdomen is tender over the pancreas and distended. Only rarely can a mass be felt in the pancreas itself. The lungs may reveal basal rales, limitation of diaphragmatic movement, and later a left pleural effusion. In a few instances, there is fullness in the left flank with costovertebral angle tenderness simulating a perinephric abscess. Tetany due to hypocalcemia may be observed rarely.

About one-fourth of the patients have transient jaundice during an acute episode of pancreatitis because of obstruction of the common bile duct by gallstones, edema of the pancreas, as a manifestation of cholangitis, or, rarely, hepatitis. Livedo reticularis has been seen on the abdomen and lower extremities. Bluish discoloration of the flanks (Grey Turner's sign) and of the umbilicus (Cullen's sign) resulting from extravasation blood pigments are well known, but may not be present frequently. On occasion, gastrointestinal bleed-

ing may accompany acute pancreatitis, usually arising high in the gastrointestinal tract adjacent to the inflamed pancreas.

4. Pathology and Pathogenesis. The underlying mechanism in the production of pancreatic inflammation is the escape of activated enzymes into the interstitial tissues. The earliest response is edema, distention of the lymphatics, and vascular engorgement of the pancreas.

Edema is likely to be more severe in the head, but it may occur anywhere in the gland, which becomes pale and indurated, and its blood vessels progressively more congested. Fluid exudes into the interlobular connective tissue and into the acini. It is an inflammatory exudate containing polymorphonuclear leukocytes and round cells. In most instances this inflammatory exudate subsides spontaneously, but in a small percentage of cases the inflammatory process proceeds to hemorrhage, necrosis and suppuration, or regresses to chronicity. Progression is partly the result of swelling of the pancreas within its capsule, a process which further increases or initiates pancreatic duct obstruction, if this is not already present, and which may enhance lymphatic congestion and vascular engorgement until vascular ischemia supervenes. Ischemia may also be the result of reflex vasospasm. As elsewhere, ischemia superimposed on an inflammatory process results in infarction. Arterial or venous thrombosis and erosion of major blood vessels by activated pancreatic ferments may result in hemorrhage into the pancreas, the retroperitoneal tissue, and even into the bowel. The most severe hemorrhage, pancreatic apoplexy, converts the gland into a boggy hematoma. Collections of blood may burrow along tissue planes into the gastrohepatic ligament, and retroperitoneally into the lesser sac and flank. In this manner, necrosis and hemorrhage may extend into the left subphrenic space, along the aorta into the pelvis and to the renal capsule.

Microscopically, varying stages of cell disintegration can be seen. The cells are pale, and their nuclei stain poorly. In the most extensively damaged regions, all structure is lost. Surrounding the areas of necrosis and demarcating them from normal tissue, are a zone of debris and a layer of inflammatory cells. Liquefaction of the dead tissue, hemorrhagic collections, and retention of blocked pancreatic secretion give rise to cystic structures. These cysts may coalesce to form larger sacs, displacing the stomach, duodenum, or colon. They are termed pseudocysts to differentiate them from true pancreatic cysts, which are formed within the pancreatic duct system and are lined with epithelial cells.

Collections of blood, digested tissues, and pancreatic secretions accumulate in the peritoneal cavity as the classic ascitic exudate of acute pancreatitis, "beef broth." Peritoneal irritation is marked in the lesser sac and at the base of the transverse mesocolon, often producing a segmental paralytic ileus of the first jejunal loop ("sentinel loop"), or a functional obstruction of the midtransverse colon ("colon-cutoff" sign). Left pleural effusion results from inflammation beneath the left diaphragmatic leaf.

Resolution may occur with fibrosis and calcification. The edema and other inflammatory changes subside during the first week of illness. Areas of necrosis are autolyzed and replaced by fibrous tissues. Cellular proliferations attempt to

restore normal glandular architecture. By the end of the second week, there may be such extensive histologic repair that the pancreas appears grossly normal. On the other hand, in the more severe forms, resolution is delayed and residual fibrosis and acinar disruption persist.

5. Mechanism of Disease Manifestation. Pain and shock are the outstanding symptoms of acute pancreatitis, with some metabolic disturbances: hyperglycemia and hypocalcemia. The pain in acute pancreatitis results from distention of the pancreatic capsule; retroperitoneal extravasations; chemical peritonitis; and obstruction or spasm in the pancreatic ducts, the extrahepatic biliary tract, and the duodenum. The systemic effects in acute pancreatitis are presumed to result from the absorption of activated pancreatic ferments and the products of pancreatic digestion into the blood stream. Shock is the outstanding systemic phenomenon. It may be so profound that death supervenes within a few hours. The shock, or "cardiovascular syndrome" in acute pancreatitis, is caused by the combined effects of the following physiological alterations:

A. Alterations in blood coagulability with hemorrhagic and thromboembolic phenomena.

B. Marked contraction of the blood volume with deficits approaching 30 percent, presumed to be the result of fluid exudation and hemorrhage.

C. Severe disturbances in the electrolyte balance, including lowering of the blood calcium, potassium, and sodium levels. The depression of calcium is due to its fixation by fatty acids in areas of fat necrosis. When the blood calcium falls below 7 mg percent, tetany may be manifested. Tetany has also been reported in a patient with normal serum calcium level, in whom it is presumed to be due to the binding of ionic calcium by fatty acids in the blood. The hypocalcemic tetany responds to the intravenous administration of calcium; the normocalcemic tetany does not, but may be relieved by the administration of parathormone. The calcium levels in pancreatitis associated with hyperparathyroidism are often normal. Alteration in lipid metabolism during acute pancreatitis is poorly understood. Hyperlipemia and grossly turbid serum may be observed frequently. There is some evidence that the pancreas is involved in the release of the physiologic clearing factor, lipoprotein lipase.

6. Diagnosis. No laboratory study can replace the clinical suspicion of acute pancreatitis, but, once suspected, several laboratory methods may be helpful:

A. *Blood Enzyme Levels.* Determination of pancreatic enzyme concentrations in the blood is the most common and useful laboratory diagnostic procedure in general use.

Serum amylase is the most conveniently measured enzyme. The amylase normally present in the blood is derived from the pancreas, the salivary glands, the liver, and other tissues. There is some evidence that the normal blood amylase is under endocrine control, is sensitive to alterations in the rate of carbohydrate metabolism, and that the site of one mechanism regulating its level in the blood appears to be the liver. The increases in serum amylase content seen during the course of acute pancreatic inflammation and/or ductal obstructions derive wholly from the pancreas, either by retrograde passage due to back pressure, or by some alteration in cellular orientation of enzyme secretion.

Elevations of serum amylase above the statistically derived normal range occur in acute pancreatitis during the first 72 hours of illness. In the milder inflammations, small rises may be present for only a few hours, making it imperative for early and frequent amylase determinations during the initial period of illness. Infrequently, a drop to normal ranges may take place rapidly, indicating early resolution. On the other hand, sudden decreases in serum amylase may reflect extensive destruction of the pancreas, with subsequent cessation of amylase production. For these reasons it is not possible to correlate the severity of the disorder with the degree of elevation of the blood amylase, nor need a normal amylase exclude the diagnosis of pancreatic disease.

Blood amylase elevations have been reported in a number of situations in which there is no pancreatic affection. These include gallbladder disease; choledocholithiasis; biliary dyskinesia; perforated peptic ulcer; intestinal obstruction; bowel transection; ruptured ectopic pregnancy; uremia; after cholangiography; after morphine-like narcotics; and after parasymphathomimetic drugs.

Serum lipase elevations tend to parallel blood amylase rises, but lipase increases occur later in the course of acute pancreatitis, and tend to persist longer than amylase elevations.

B. Urinary Enzyme Levels. Elevation of the urinary amylase concentration has been used to diagnose acute pancreatitis. Amylase is excreted by the kidney as a threshold substance. Thus, elevations in blood amylase are reflected in the urine, although the appearance of rises in the latter may be delayed by the presence of renal insufficiency. Although it has been claimed that elevation of urinary amylase levels may persist long after the disappearance of high concentrations of amylase in the blood, many have found such wide variation of urinary amylase concentration, even in the normal subject, that the value and reliability of this determination have been seriously questioned.

C. Blood Chemical Determinations. Transitory glycosuria and hyperglycemia have been observed in about 10 percent of cases of acute pancreatitis, and in acute exacerbations of chronic pancreatitis. We have found glycosuria, hyperglycemia, and/or abnormal glucose tolerance in 25 percent of an unreported series of more than 100 patients with acute pancreatitis. Hyperglycemia without glycosuria is particularly suggestive of pancreatic inflammation.

Lowered values of serum calcium have been reported to persist for a fortnight or longer, and are thought to have diagnostic significance in patients with acute pancreatitis who are seen after the blood amylase has returned to normal. This suggestion must be judged in light of the low serum calcium values which have been reported in perforated peptic ulcer. Blood calcium depressions to values below 7.0 mg percent have been associated with tetany and fatal outcome.

Lowered potassium concentrations to levels below 4.0 mEq/L have been

observed and attributed to lowered intake, excessive urinary loss, loss by nasogastric suction, and to alteration in adrenocortical function.

D. X-Ray Manifestations. The x-ray manifestations of acute pancreatic inflammation include: 1) haziness in the flat film of the abdomen; 2) obliteration of the psoas outline; 3) elevation of the left diaphragmatic leaf; 4) paralytic ileus with its manifestation of the "sentinel" jejunal loop in the left upper quadrant; and 5) basal pneumonitis, pleurisy, or pleural effusion in the left chest.

Cholecystography (oral), usually offers little assistance in acute pancreatic inflammation except to demonstrate calculi, because of concomitant impairment of gallbladder function.

E. Peritoneal Tap. Peritoneal tap may be an important useful aid in diagnosis.

7. Treatment. The immediate problem of management of acute pancreatitis is the choice between medical and surgical treatment. When the diagnosis has been established, the overwhelming evidence based on comparison between the mortality of patients treated surgically, which ranges from 35 to 78 percent, and the mortality of patients treated medically, which appears to vary between 10 and 20 percent, favors medical management.

In those patients in whom laparotomy has been done because of inability to make a positive diagnosis, surgical manipulation should be reduced to a minimum: drainage of the lesser sac or a diversionary operation on the biliary tract, cholecystostomy or choledochostomy in patients with obvious biliary tract disease.

Medical treatment should be energetic whether the clinical picture is mild or severe, for it is not possible to predict which cases will regress rapidly and which will progress to critical complication. Therapy in the acute stage is directed toward: A. treatment of pain; B. treatment of shock and electrolyte imbalance; C. management of carbohydrate metabolism disturbances; D. treatment of ileus and control of distention; E. prevention of suppuration; F. suppression of pancreatic secretion and neutralization of ferment activity; G. management of surgical complications; and H. prevention of recurrence.

Management begins with complete bed rest, and nothing given by mouth until the acute episode subsides. Pain should be relieved promptly by parenteral injection of narcotics; meperidine is preferable, because of the tendency of morphine to cause contraction of the sphincter of Oddi and consequent rise in intraductal pressure. Shock calls for replacement by blood, plasma, albumin and plasma expanders sufficient to maintain normal blood volume, blood pressure, and renal function. Plasma electrolyte derangement requires careful attention to sodium, potassium, and chloride replacement, especially when nasogastric suction is being performed. Glucose must be administered cautiously, since there may be deficient insulin secretion of the pancreas. Ileus and abdominal distention are combated by stopping oral intake and by nasogastric suction, which is the prime approach to suppressing pancreatic secretion. In addition, anticholinergic drugs as Atropine[®], and the newer synthetics which

include Bantline®, should be administered parenterally every three to four hours. Suppuration may be prevented by the use of broad spectrum antibiotics. The liberal use of antibiotics has been useful in preventing abscess formation. Cortisone® and ACTH have been recommended in acutely sick patients, and good results are reported. Our own experience would limit these drugs to patients with acute pancreatitis who have adrenocortical deficiency or overwhelming pancreatic necrosis.

Management of Surgical Complications. The surgical complications which arise in acute pancreatitis include abscess, which necessitates drainage; pancreatic fistula; pseudocyst, which requires diversion into the gastrointestinal tract; and the complications inherent in coexisting biliary tract disease.

Pancreatic abscess is a rare complication since the advent of chemotherapy. This may occur, as previously stated, in the parenchyma, lesser sac, and in the left subphrenic space. The surgical problem is not drainage *per se*, because this ordinarily can be done without technical difficulty, but rather it is the possibility of subsequent formation of a pancreatic fistula with the attendant deleterious effects of electrolyte loss, disturbance in metabolism, and maceration of the skin.

Pancreatic fistulas have been treated by sclerosing agents; total excision whenever possible; implantation into the stomach or jejunum; and by fistulo-jejunostomy in Roux-Y fashion.

Pancreatic cysts or pseudocysts are treated when their size and situation produce symptoms by encroachment on other organs. It is remarkable how often large pseudocysts will suddenly disappear without operation. The ideal procedure would be extirpation by excision, but this is not always feasible, especially in head lesions, and is not always desirable because of the extent of surgery involved. Simple evacuation and external marsupialization have been discarded because of the high incidence of recurrence, and because of the frequent development of external pancreatic fistulas. Internal drainage may be accomplished by anastomosis of the cyst to the stomach, the duodenum or jejunum, or by the generally accepted procedure of choice, a cystojejunostomy using a Roux-Y anastomosis to eliminate the hazard of intestinal regurgitation into the cyst cavity.

References

- Dreiling, D. A., and Janowitz, H. D.: The Pathophysiology of the Pancreas in the *Advances in Internal Medicine*, Dock, W., and Snapper, I., eds., The Year Book Publishers, Inc., Chicago 1955, VII:65.
- : Exocrine Pancreatic Secretion, Effects of Pancreatic Disease, *Amer J Med* 21:98, 1956.
- Machella, T. E.: Medical Aspects of Pancreatitis, *JAMA* 169:1571, 1959.

CHRONIC PANCREATITIS

I. Varieties. The clinical features of the classic form of chronic relapsing pancreatitis are well known, especially since their description in America by Comfort and his associates. Predominantly a male disorder (ratio of 2.5:1),

occurring in the 4th decade and after, it usually manifests itself with recurrent attacks of upper abdominal pain in the area of distribution of pancreatic pain. Often, this pain is its only manifestation, but the chronicity, recurrences, and failure to respond to simple analgesics often completely incapacitate these unfortunate people, and all too frequently leads to their addiction to morphine or meperidine. When the destructive inflammatory changes within the gland are extensive enough, the classic metabolic defects of this disease ensue: calcification; impaired carbohydrate metabolism (a true pancreatic diabetes); and external pancreatic insufficiency, leading to malabsorption and malnutrition.

In this setting it is conventional to emphasize two associated disorders: chronic gallbladder disease with stones, and chronic alcoholism.

Of the first of these, cholecystic disease, clinical or radiographic evidence may be present in perhaps 25 percent or less of the patients, depending on where the series is collected. Of a considerable number of patients with chronic pancreatitis (especially in large city hospital populations), up to 40 percent may also be chronic alcoholics. There are many interesting and puzzling aspects of this association. Fibrosis of the pancreas may frequently accompany alcoholic Laennec's cirrhosis, yet outspoken chronic relapsing pancreatitis in our experience rarely accompanies unquestioned portal cirrhosis with portal hypertension.

A. *"Silent" Pancreatitis.* A variant of this disease or diseases, is the patient who is accidentally discovered to have extensive calcification of the pancreas during life when a flat plate of the abdomen is taken for any reason at all. This has been seen in persons without antecedent history of biliary disease or alcoholism, who have had no episode remotely resembling acute pancreatitis in the past. Not only may they be clinically quite well, but study of their external pancreatic function, fat balance studies, and glucose tolerance tests reveal no significant impairment of either the exocrine or endocrine pancreas. One may wonder whether this may be properly considered "pancreatitis" at all; yet profound pathologic changes may be presumed to have taken place in the gland. The calcification is not simply precipitation of stores within ducts or duct-like structures, but would appear to be a diffuse calcinosis of the gland itself.

Such a conclusion seems justified from the discovery at postmortem of interstitial inflammatory or focal pancreatitis in a wide variety of clinical conditions, without antecedent symptomatology to suggest acute pancreatitis during life. This finding, however, does not justify the indiscriminate diagnosis of pancreatitis in all people with ill-defined upper abdominal pain or digestive disturbances.

B. *Hereditary Pancreatitis.* The nature of pancreatitis has been further enlarged by the studies of Gross and Comfort of a hereditary variety, occurring in several kinships, usually starting in childhood or early adult life which behaves as a non-sex-linked Mendelian characteristic. Their contribution to the genetic aspects of the disease has disclosed also a heritable defect in the pattern of urinary amino acid excretion in these patients and their relatives: an increased excretion of the amino acid lysine. At present, the relationship be-

tween the pancreatic disorder and the increased amino aciduria is unknown, but it does stress the genetic and metabolic aspects of the disease.

C. Hyperparathyroidism, Hyperlipemia and Pancreatitis. The possible metabolic nature of this group of disorders has been further enlarged by the association of pancreatitis with two other metabolic disorders: hyperparathyroidism and essential hyperlipemia.

2. Diagnosis. To make the diagnosis clinically, one must bear this entity in mind in all situations of obscure upper abdominal discomforts; on the other hand, we cannot use chronic pancreatitis as a catch-all for every upper abdominal undiagnosed pain. In the truly "silent" pancreatitis, the history will offer no assistance, of course, whereas in the other clinically significant varieties the history is a starting point. The classic features are recurrent upper abdominal pain, distributed over the area of radiation of the pancreas, often to the back. The picture of severe prostrating pain of acute pancreatitis rarely occurs in chronic pancreatitis, although the patients are frequently disabled. The history of chronic biliary disease or of chronic excessive consumption of alcohol may be helpful. In view of the other varieties of chronic pancreatitis, history-taking must now be directed toward evidence of a familial nature. A history suggestive of hyperlipemia in the family or in the patient, or features suggestive of hyperparathyroidism, should be specifically looked for. When the inflammation of the pancreas is so severe as to lead to disturbances in the external secretion of the pancreas, one may begin to elicit features of the disease. Malnutrition is manifested first by calorie loss, with consequent weight loss; and secondly the passage of large, bulky, foul-smelling stools, containing large amounts of neutral fats. This is also accompanied by evidences of malabsorption of fat-soluble vitamins; however, osteomalacia and evidences of hypoprothrombinemia are exceedingly rare.

Physical examination may disclose nothing. In other instances there may be evidence of appreciable weight loss. If the patient has hyperlipemia, there may be evidence of xanthomata. Abdominal examination may disclose nothing, or there may be tenderness over the area of the pancreas; in rare instances a mass such as a pseudocyst may be found in the pancreas. In general, the history and the laboratory determinations, rather than the physical findings, establish the diagnosis.

Adjunctive Aids. A plain film of the abdomen may disclose calcification within the pancreas. Despite the considerable disagreement, it may be said that these calculi are either in the ducts or in the acinar tissue itself. The bulk appear to be within acinar tissue. A small bowel x-ray is also useful in patients who have evidence of malabsorption; for patients with a chronic pancreatitis have a normal small bowel pattern, in contrast to disordered motor pattern seen in patients with idiopathic sprue.

Chemical studies are significant in diagnosing chronic pancreatitis. If the disease is far advanced, there is evidence of disturbance of carbohydrate metabolism: elevated fasting blood sugar, an abnormal glucose tolerance test, and glycosuria. This feature, however, may be missing in some instances. The

study of blood enzymes of pancreatic origin is not particularly helpful in the diagnosis. During acute exacerbations of chronic pancreatitis, there may be a rise in serum amylase, but usually the serum amylase level is either normal or low; the same is true of lipase. Numerous newer enzyme determinations have been proposed, but none of these has yet met satisfactory clinical judgment. Evidence of severe marked impairment of external pancreatic secretion may be sought in the examination of the stools, both grossly and by chemical tests when there is steatorrhea composed essentially of neutral fat. About 30 percent of our patients with chronic pancreatitis have this far-advanced evidence of external pancreatic secretion. Therefore, when the patient does not have calcification or diabetes or steatorrhea, one is hard put to make the diagnosis of chronic pancreatitis, or at least to substantiate it when it is suspected clinically, unless there is direct study of the external secretion of the pancreas.

Fat and oleic acid labeled with I^{131} is useful when the differential diagnosis lies between pancreatic and idiopathic steatorrhea. Here, the published evidence indicates that the absorption is impaired in the presence of external pancreatic insufficiency, but this test can logically be applied only to those patients presenting advanced evidence of external pancreatic insufficiency. Since a large number of patients with chronic pancreatitis would be missed if this were relied on, we place much emphasis on the study of the external secretion of the pancreas by direct duodenal intubation; the secretin test:

This consists of intubating the duodenum by a double-lumen tube, which effectively separates pancreatic secretion stimulated by secretin from contamination by hydrochloric acid. A standard dose of secretin is used (1 unit per kilogram of body weight), and the secretions are collected for a period of 80 minutes, at the end of which time response to secretin has been dissipated. On the basis of extensive study of normal persons, statistical levels have been established for a normal response. At present, there is no evidence of a syndrome of hypersecretion of the pancreas. Therefore, the statistical norms have been devoted to establishment of the lower limits of the normal. When the values have been adjusted to the body weight, there is considerable reduction in scatter. These values include volume flow, which is essentially greater than 2.0 cc per kg of body weight in normals, bicarbonate concentrate of above 90 mEq/L, with a wider variation in amylase which may be anywhere from 6 to 9 units of amylase per kg of body weight. We have observed that reduction in flow may occur in some patients with chronic pancreatitis, but that their striking defect is an inability to elaborate a fluid of high bicarbonate content as well as depression of enzyme output. From these criteria the external secretion of the pancreas may be assessed for volume flow, bicarbonate, and enzyme (amylase) with a high degree of reproducibility and reliability.

Chronic pancreatitis can be suspected clinically only on the basis of recurrent upper abdominal pain associated with malnutrition, diabetes, and steatorrhea. The physical findings are not particularly helpful. The laboratory findings of pancreatic calcification, impaired carbohydrate tolerance, and increased excretion of fat in the stool are all supportive. A final diagnostic statement as to external pancreatic function, depends on the study of the external function directly by collection of pancreatic juice under standard conditions. It remains to be determined whether the addition of the hormone pancreozymin will improve the diagnostic value of the secretin test. An important part, however, in

the current secretin test, is the cytologic examination of the fluid, since the picture of chronic pancreatitis may often be mimicked by a carcinoma of the body of the pancreas. Since, indeed, carcinoma may exist in the presence of chronic pancreatitis, we have found the examination of the cells of this fluid extremely helpful.

3. Therapy. The treatment of chronic pancreatitis is difficult, far from standardized, and often disappointing. Medical therapy, which leaves much to be desired, includes a high-calorie, high-protein, low-fat diet supplemented by vitamins. Frequent small feedings are advocated to minimize pancreatic secretion. Alcohol is interdicted because of its known and unknown effect on pancreatic secretion, and its action on the duodenal mucosa and sphincter. Substitution therapy includes pancreatic extract in patients with steatorrhea. Pancreatin sometimes strikingly reverses the symptoms of external pancreatic enzyme deficiency, but extremely high doses must be used (3 to 5 gm with each meal). Recently other forms of pancreatic extract, Cotazym® for example, have been widely publicized. In patients with gastric hypersecretion, an antacid minimizes acid inactivation of the replacement therapy.

Despite all forms of medical treatment, some patients continue to have excruciating pain, progressive weight loss, and progressive mental and physical deterioration. Surgery is a final, often desperate, therapeutic attempt, and the many procedures that have been advocated are an index of the diversity of opinion about the pathogenesis of symptoms, and of the indifferent success of such treatment.

The first point of attack is the underlying biliary tract disease which may be present. The initial operation is the logical time to explore the common duct and to determine whether stone or inflammation is causing obstruction at the papilla.

Procedures for obstruction of the distal common duct are dictated by the size and type of obstruction. Stones are removed and prolonged drainage of the common duct is instituted. For ductal stenosis, choledochoduodenostomy or a Roux-Y choledochojejunostomy is thought to be superior to T-tube drainage, since the former completely divert the biliary flow from the pancreatic tract and by-pass lesions at the papilla. Roux-Y anastomosis minimizes retrograde regurgitation of intestinal contents into the biliary tree, and therefore may be accompanied by a lower incidence of cholangitis and cholangiolitis and resultant biliary cirrhosis, than does direct ductal-enteric union.

Functional and organic obstruction of the perianipular region may be relieved by operations on the sphincter of Oddi by transduodenal sphincterotomy.

Gastrointestinal diversion may be necessary because of mechanical obstruction of the duodenum, resulting from extensive fibrosis or from actual encroachment by a large cyst in the head of the pancreas.

The direct surgical attack on the diseased pancreas includes operations designed to treat the complications of the inflammatory process; procedures

attempting to eradicate etiologic factors which initiate the recrudescences of inflammation; and measures aimed at removing the diseased tissue itself.

Purulent collections within the pancreas, the lesser sac, and the left subphrenic space are treated by incision and drainage. Pancreatic cysts or pseudocysts require surgery only when, because of size or location, symptoms result from encroachment on adjacent viscera.

A number of procedures have been suggested to overcome pancreatic duct obstruction, but have not had sufficient clinical trial to warrant conclusions on their value. Among these are pancreaticolithotomy; ligation of the main pancreatic duct to completely destroy the acinar tissue; and transection of the main pancreatic duct, followed by immediate reanastomosis to the duodenum. Relief of pancreatic duct obstruction in a retrograde fashion, has been attempted by implanting the tail of the pancreas or the distal end of the pancreatic duct into a loop of upper jejunum. DuVal's caudal decompression of the pancreas seems to be a sensible solution to the problem of obstruction in the duct system distal to the sphincter, when this can be demonstrated convincingly.

Pancreatectomy, the final, desperate step is reserved for those incapacitated persons in whom all other measures have failed. Resection of the left half of the pancreas in those rare cases in which the disease is limited and more severe in the tail presents no technical difficulty, and the results are gratifying. In most patients, however, the disease process is more diffuse and most severe in the region of the head. Since distal pancreatectomy is of doubtful benefit in such cases, total pancreatectomy is required. The problems posed by diabetes and metabolic disturbances after pancreatectomy are more easily managed than the chronic pancreatitis itself.

References

- Gross, J. B., and Comfort, M. W.: Chronic Pancreatitis, *Amer J Med* 25:596, 1956.
Janowitz, H. D., and Dreiling, D. A.: Pancreatitis in *Disease-a-Month*, The Year Book Publishers, Inc., Chicago 1959.
Comfort, M. W., Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis: Study of 29 Cases without Associated Disease of Biliary or Gastrointestinal Tracts, *Gastroenterology* 6:239, 376, 1946.

ANOMALIES

1. Annular Pancreas. Annular pancreas is a congenital anomaly caused by improper rotation of the ventral pancreatic bud and faulty fusion of this bud with the dorsal pancreatic anlage. There results a deforming ring which completely encircles the second portion of the duodenum. The ring consists of normal pancreatic tissue, though in some cases there may be evidence of recurrent pancreatic inflammation. The pancreatic ductal system is always grossly aberrant, major ducts not infrequently coursing through the ring itself before emptying into the duodenum. Duodenal obstruction may or may not be present, but the hazard of impaction of ingested foodstuffs resulting in high intestinal obstruction presents a hazard.

Annular pancreas may be completely asymptomatic. When symptoms do occur, the onset may be in childhood or in late adult life. Complaints are the result of duodenal stasis due to luminal encroachment or to food impaction. Infrequently, increased duodenal pressure results secondarily in acute pancreatitis and even obstructive jaundice. The symptoms range from mild attacks of postprandial discomfort with eructation and nausea, to violent episodes of acute epigastric pain associated with nausea, protracted vomiting, upper intestinal distention, and obstipation.

The diagnosis is made by roentgenography. Flat films of the abdomen reveal a large distended stomach and upper duodenum. A barium swallow will locate a smooth constricting ring in the second portion of the duodenum.

For those patients with symptomatic annular pancreas or with the complications of this anomaly, i.e., pancreatitis or obstructive jaundice, surgical relief of duodenal obstruction is imperative. Direct operative transection of the ring is contra-indicated by a high morbidity and mortality due to acute traumatic pancreatitis. Relief of duodenal obstruction is best accomplished by a "by-pass" procedure—duodenojejunostomy when feasible or simple gastrojejunostomy. The relief of symptoms is prompt and permanent.

The clinical picture in annular pancreas and the pathogenesis of symptomatology closely resemble the findings in symptomatic superior mesenteric artery syndrome. In the latter condition, duodenal obstruction results from compression of the fourth portion of the duodenum between the superior mesenteric artery and the spine. Thus, both annular pancreas and superior mesenteric artery syndrome produce duodenal obstruction; both are complicated occasionally by acute pancreatitis resulting from increased duodenal pressures. Both are relieved by "by-pass" procedures. Only roentgenography and exploration can differentiate these congenital anomalies.

References

- Ravitch, M. D., and Woods, A. C., Jr.: Annular Pancreas, *Ann Surg* 132:1116, 1950.
Dreiling, D. A., Kirschner, P. A., and Nemser, H.: Chronic Duodenal Obstruction: A Mechano-vascular Etiology of Pancreatitis. I. Report of Six Cases Illustrating this Clinical Variety, *Amer J Dig Dis* 5:991, 1960.

2. Ectopic (Aberrant) Pancreas. Ectopic (aberrant) pancreas (pancreatic rests, pancreatic heterotopia) has been described in the stomach, in the duodenal, jejunal and ileal wall, in the colon, mesentery, omentum, spleen, gall-bladder, and biliary ducts. The true incidence of this often asymptomatic anomaly is unknown.

The ectopic tissue occurs in single or multiple nodules, usually less than one-half inch in diameter. Obstructive symptoms from nodules of this size are extremely rare. The ectopic tissue consists of histologically normal parenchyma. Either acinar or islet tissue may predominate, but usually both are present and potentially functional.

The clinical significance of pancreatic heterotopia depends upon size, location, physiologic activity, and the complications which may arise within the

aberrant tissue, *viz*: A. inflammation; B. neoplasia; C. ulceration with or without perforation; D. massive or occult gastrointestinal hemorrhage; and E. intussusception.

The diagnosis of ectopic pancreas remains elusive. Though occasionally suspected in patients with inexplicable persistent spontaneous hypoglycemia; in patients with bizarre intestinal complaints, hemorrhage, and perforation; and in patients with unusual small intestinal roentgen mass, ulceration, or blockage, ectopic pancreas most frequently is an operative finding.

Pancreatic heterotopia is best treated by local excision where feasible. Wider extirpation is obligatory in those patients in whom histologic study of the resected nodule indicates malignancy. The abdomen always should be thoroughly explored for the areas of aberrant pancreas.

References

Barbosa, J. J. deC., Docherty, M. B., and Waugh, J. M.: Pancreatic Heterotopia: Review of the Literature and Report of 41 Authenticated Cases of which 25 were Clinically Significant, *Surg Gynec Obst* 82:527, 1946.

PANCREATIC NEOPLASMS

Neoplasms in the pancreas may be benign (cyst, pseudocyst, adenoma, cystadenoma), or malignant (carcinoma, sarcoma, cystadenocarcinoma, islet cell carcinoma). Enlargements of the pancreas may also be due to infiltrations by Hodgkin's disease, lymphoma, and even by fat lipomatosis.

In pancreatic tumefactions the diagnostic clues and clinical picture depend upon the site and size of the mass and upon its secondary physiologic effects. Thus, masses in the body and tail of the pancreas may progress to large dimensions before they are palpable, and with little disturbance in body economy save the onset of mild diabetes. As the tumor extends to the body of the pancreas, severe constant boring midback pain in addition to diabetes becomes of diagnostic import. Neoplasms of the head of the pancreas manifest themselves by symptoms of upper intestinal obstruction, jaundice, and external pancreatic secretory deficiency. There exist, of course, types of tumefaction within the pancreas, in which location and size are of little importance, but rather these tumors are known by their metabolic effects, *viz*: 1. insulin producing islet tumors (insulinomas and islet cell carcinomas); 2. the non insulin-producing ulcerogenic tumors (non-Beta cell islet adenomas, Zollinger-Ellison adenoma); and 3. the rare insulin-producing ulcerogenic islet adenomas.

1. Cysts. Cysts of the pancreas are rare lesions and may be grouped in five categories:

A. *Congenital* (simple cysts, polycystic disease, dermoid cysts, fibrocystic disease).

B. *Inflammatory* (retention, pseudocysts).

C. *Parasitic*.

D. *Traumatic* (direct and indirect contusion, operative injury).

E. *Neoplastic* (cystadenoma, cystadenocarcinoma, teratoma).

Congenital cysts are smooth walled cavities lined by simple epithelium. Pan-

creatic ferments may or may not be present in the cyst fluid. With the exception of dermoid cysts, congenital cysts rarely produce symptoms. Any cyst, of course, may by progressive enlargement impinge upon the neighboring intestinal viscus, and in this way induce symptoms requiring surgical relief.

Pseudocysts and retention cysts are complications of acute inflammatory processes within the pancreas, resulting in a loss of continuity of duct epithelium, or a simple blockade of the duct itself. The latter produces a progressive dilatation of the distal duct system, the retention cyst which thus is lined by ductular epithelium; the former results in extravasation of activated pancreatic juice which dissects and digests the surrounding tissue producing a cystic cavity not lined by true epithelium, hence, a pseudocyst. Such pseudocysts may burrow irregularly into the retroperitoneal tissues, into the chest, and into the mediastinum. Their presence is indicated by the failure of symptoms to subside during the first week after onset of acute pancreatitis by the persistence of abdominal pain, tenderness, fever, leukocytosis, hyperamylasemia, and abnormal external pancreatic secretion. Although in many instances a pseudocyst may resolve by spontaneous rupture into the pancreatic duct system, in most cases the persistence of pancreatic inflammation, the danger of superimposed infection resulting in pancreatic abscess, and the impingement on the stomach, duodenum or common duct resulting in high incomplete intestinal obstruction or jaundice, requires surgical decompression of the pseudocyst.

Traumatic cysts arise in areas of pancreatic contusion (direct and contracoup) and pancreatic lacerations which sever a main duct. Peritoneal signs may appear immediately, requiring exploration, but frequently the clinical course is more obscure and symptoms appear only when the cyst size has progressed to such dimension that pressure is produced on the neighboring hollow viscus.

Cystadenoma and cystadenocarcinoma are multiocular tumors comprising cystic and adenomatous tissues. The benign neoplasm, cystadenoma, produces symptoms only when growth causes displacement of a neighboring viscus. Cystadenoma, however, is a potentially malignant tumor, degenerating into cystadenocarcinoma which rapidly disseminates to the peritoneum, the liver, and to the lung. Thus, multicystic fleshy tumors should be extirpated in toto whenever feasible.

The treatment of cystadenoma and cystadenocarcinoma is total extirpation. For lesions of the body and tail of the pancreas this is accomplished without surgical difficulty, requiring only sacrifice of the spleen. Cystic tumors of the head can be resected by a Whipple's operation which requires simultaneous partial gastrectomy, removal of the duodenum, and transection of the common duct in addition to pancreatic resection.

Traumatic cysts and pseudocysts are best treated by extirpation when feasible. While resections of the left pancreas may be justified for these benign conditions, it is doubtful whether the formidable operation of resection of the head should be undertaken to eradicate these lesions. Pseudocysts so situated, as well as those in which total excision presents technical difficulty, are treated

by a drainage procedure. External drainage (marsupialization), though technically simple, has been abandoned by most surgeons because of the high incidence of recurrence and of persistent external pancreatic fistula. Internal drainage which has the advantage of returning enzyme-containing pancreatic secretion to the gastrointestinal tract, can be accomplished by anastomosis of the cyst to the stomach, to the duodenum, or to the jejunum. The procedure of choice in most clinics is to anastomose the cyst to the jejunum in Rouxen-Y fashion, thereby minimizing the danger of recurrent inflammation in the cyst due to the retrograde passage of intestinal content.

2. Adenomas. Adenomas of the pancreas are relatively frequent benign tumors, often found incidently at postmortem examination, and rarely growing to significant size to produce symptoms. Ordinarily, pancreatic adenomas are of little clinical significance, unless they are complicated by either malignant degeneration or hormonal dysfunction.

Histologically, pancreatic adenomas consist of acinar, or islet tissue, or mixtures. Those predominantly islet tissue may be further subdivided into alpha, beta, delta, and undifferentiated islet cell tumors.

Among the hyperfunctioning islet cell tumors, two large clinical syndromes have been described:

A. *Beta cell tumor* (spontaneous hypoglycemia), which is characterized by the symptomatology of hyperinsulinism.

B. *Non-beta cell tumor* (Zollinger-Ellison syndrome), which is characterized by prodigious gastric hypersecretion and recurrent atypical peptic ulceration.

There has been no documented clinical report of a functioning alpha (glucagon producing) cell tumor, but theoretically, the existence of such a syndrome appears likely.

The beta cell functioning tumors may be benign or malignant. The physiologic syndrome is due to the excessive and erratic production of insulin. Excessive concentrations of this hormone have been demonstrated in the tumor proper, in metastatic tissue, in the blood, and in the urine. Patients with functioning beta cell tumors usually satisfy a triad proposed by Whipple: 1) low fasting blood sugar; 2) onset of attacks of hyperinsulinism (sweating, tremor, tachycardia, loss of consciousness, convulsions) after prolonged fasting; 3) prompt relief of symptoms upon the oral administration of sugar.

There has been great interest recently in a group of patients with functioning pancreatic adenomas in whom the cell type is neither alpha nor beta. Considerable controversy exists as to which element within the islet, i.e., delta, gamma, or other is responsible for a complex syndrome characterized by:

- 1) Prodigious gastric hypersecretion beyond the ranges of ulcer patients.
- 2) Persistent and recurrent peptic ulceration not ameliorated by traditional medical and surgical therapies.
- 3) Idiopathic severe diarrhea and steatorrhea.
- 4) Marked disturbances in electrolyte metabolism, i.e., potassium and calcium—hypokalemia, and hyperealemia.

The pathogenetic basis for these metabolic disturbances was obscure until a gastrin-like substance was recently isolated from non-beta cell tumors by Gregory et al., and Osborne et al. Under the influence of this hormone there is prolonged and excessive secretion of acid, electrolytes, and fluid by the gastric mucosa and, perhaps, even hyperplasia of the parietal cell mass. The increased acidity in the small intestine contributes to the ulcer diathesis and to the diarrhea and/or steatorrhea, which is seen in Zollinger-Ellison syndrome. The loss of electrolyte and fluid in the excessive gastric secretion is the physiologic basis for the severe electrolyte disturbances reported in this group of patients. Still unexplained are documented cases with Zollinger-Ellison syndrome in which the clinical picture has appeared without pancreatic adenoma, and also those cases in which adenocarcinoma of the pancreas is found rather than pancreatic adenoma. Werner and his associates consider the Zollinger-Ellison syndrome in such patients to be part of a congenital disorder of the entire endocrine system. They have published family histories establishing an association of atypical peptic ulceration; pancreatic adenoma, with adenomas in the pituitary, the thyroid, and parathyroid. Werner believes that the pancreatic adenoma is coincidental, and that the gastric hypersecretion and atypical peptic ulceration result from a congenital gastrointestinal defect. Others have been impressed by the multiplicity of adenoma, both in the pancreas, and in other endocrine glands in these patients.

The treatment of symptomatic pancreatic adenoma, malignant or hyperfunctioning, is total extirpation. The surgical problem in these patients is that the smallness of the lesion renders disclosure by palpation, extremely difficult even to the experienced surgeon. Another difficulty is the high incidence of multiplicity of lesion.

In pancreatic hyperinsulinism, total excision of the hyperfunctioning beta cell tumefactions will result in complete cure unless functioning metastatic tissue is overlooked. It was hoped that beta cell destruction with alloxan would alleviate complaints in this group of patients, but clinical trial has not been rewarding. An occasional patient with spontaneous hypoglycemia will present no tumor at exploration. In such instances, subtotal resection of the pancreas has been justified by the pathologic report of diffuse beta cell hyperplasia in islets of normal size.

Excision of pancreatic adenoma for relief of Zollinger-Ellison syndrome has met with indifferent success. There is insufficient clinical experience to determine whether or not this failure is due to multiplicity of lesion. Zollinger advocates total gastrectomy. Complete removal of the acid producing gastric secretion will, of course, remove the physiologic basis for persistent and recurrent atypical peptic ulceration. Whenever a pancreatic tumor is found it should be extirpated; in the absence of palpable tumor some have advocated subtotal pancreatectomy.

3. Lipomatosis. An unusual form of benign pancreatic tumefaction is lipomatosis of the pancreas. This occurs in two clinical varieties: *A. fatty infiltration of the pancreas*, in which fat is deposited mainly in the interlobular

connective tissue; and *B. lipodystrophy of the pancreas*, in which fat appears within the acinar cells. In both forms there is a disturbance in pancreatic secretion with moderate depression of enzyme function. Fatty infiltration of the pancreas occurs in the extremely obese patient. The lesion is completely reversible. Lipodystrophy, on the other hand, is a lesion of obscure etiology occurring in thin middle aged adults. Its clinical course is poorly understood. Like fatty infiltration of the liver, progression may result in parenchymal atrophy (idiopathic pancreatic atrophy) and fibrosis. Such progression is accompanied by malnutrition, inanition, and death. There is no known therapy for lipodystrophy.

4. Carcinoma. Carcinoma of the pancreatic glandular tissue (adenocarcinoma, duct cell carcinoma), presents as three clinical syndromes according to the location of the neoplasm:

A. Body and tail.

B. Head.

C. Periapillary lesions.

In lesions of the body and tail, the onset of symptoms is insidious. The clinical picture includes weakness; weight loss; midback pain; onset of mild diabetes; and, occasionally, recurrent idiopathic thrombophlebitis. The diabetes is due to destruction of islet tissue; the pain, to infiltration and metastases to the celiac nodes; the thrombophlebitis has no known physiologic basis.

Tumors of the head of the pancreas manifest themselves by obstructing the main pancreatic duct, the duodenum or the upper jejunum, and also by infiltrating the major mesenteric vessels. The symptomatology, therefore, in addition to weakness; weight loss; and anemia, includes nausea; vomiting; diarrhea and/or steatorrhea; and melena, either gross or microscopic. Exsanguinating hemorrhage may occur as a terminal event.

Cancer of the periapillary area includes carcinomas arising in the pancreas, in the terminal common duct, and those originating in the duodenal mucosa of the papilla of Vater. Because of the strategic position of such tumors, it is obvious that the clinical picture must be preceded by obstructive jaundice. This jaundice is often painless, intermittent but progressive, and usually associated by progressive enlargement of the gallbladder (Courvoisier gallbladder). The development of the Courvoisier gallbladder is possible only in the patient without significant preexistent inflammatory disease of the gallbladder. It should not be considered pathognomonic of periapillary tumor, because a Courvoisier gallbladder can occur with obstructions higher up in the common duct as well as with obstructions in the cystic duct.

It thus becomes apparent that clinical symptoms, and hence diagnosis, occur late in the natural course of all cancers of the pancreas, except periapillary malignancies which are heralded early by obstructive jaundice. This explains the dismal results (five-year survival of less than 5 percent) achieved by even the most extirpative procedures.

Cancers of the body and tail of the pancreas present no technical surgical

problems. In the absence of distant metastases and local infiltration of the major vessels, removal can be accomplished by subtotal pancreatectomy and splenectomy, with preservation of the head of the pancreas.

Cancer of the pancreatic head and of the periampullary region requires more extensive surgery. The classical procedure was designed by Whipple and includes resection in continuity of the distal stomach, the duodenum, the distal common duct, and the right half of the pancreas. Restoration of gastrointestinal continuity is then accomplished by implanting the proximal common duct and the distal pancreatic duct into the proximal jejunum; a gastrojejunostomy is constructed distal to these implantations. Leakage or stenosis of such an implanted pancreatic duct has resulted in troublesome morbidity and mortality, leading many surgeons to extend the operation to total pancreatectomy, by resecting the body and tail of the pancreas and the spleen.

Major pancreatic resection (Whipple procedure, total pancreatectomy), even in the hands of the most experienced surgeon, is attended by serious morbidity and a mortality of at least 25 percent. Whether such a procedure is justified for tumors (head of pancreas), which yield a five-year survival of less than 5 percent, has been the subject of considerable controversy. On the other hand, operative resection for periampullary cancer, where the reported five-year survival rate has been as high as 40 percent, has been almost universally accepted as the therapy of choice.

References

- Howard, J. M., Moss, N. H., and Rhoads, J. E.: Hyperinsulinism and Islet Cell Tumors of the Pancreas with 398 Recorded Tumors, *Surg Gynec Obstet* 90:417, 1950.
- Warren, K. W.: Management of Pancreatic Injuries, *Surg Clin N Amer* 31:790, 1951.
- Osborne, M. P., Brown, M. E., and LeCompte, P. M.: Uleerogenic Non-Beta Cell Pancreatic Islet Carcinoma Studies on the Extraction and Assay of a Possible Gastric Secretagogue, *Amer J Surg* 100:48, 1960.
- Gregory, R. A., Tracy, H. J., French, J. M., and Sircus, W.: Extraction of a Gastrin-Like Substance from a Pancreatic Tumor in a Case of Zollinger-Ellison Syndrome, *Lancet* 1:1046, 1960.
- Letton, A. H., and Wilson, J. P.: Application of the Roux en Y Anastomosis to Diseases of the Pancreas, *J Int Coll Surg* 32:123, 1959.
- Mallet-Guy, P., and Michoulier, J.: Proximal Pancreatectomy in the Treatment of Pseudocysts of the Pancreas, *Lyon Chir* 54:708, 726, 1958.
- Murphy, R. F., and Hinkamp, J. F.: Pancreatic Pseudocyst: Report of Thirty-Five Cases, *Arch Surg* 81:564, 1960.
- Rodgers, F. A.: Islet Cell Tumors of the Pancreas and Hyperinsulinism, *Amer J Surg* 99:268, 1959.
- Whipple, A. O.: Radical Surgery for Certain Cases of Pancreatic Fibrosis Associated with Calcareous Deposits, *Ann Surg* 124:991, 1946.
- Zollinger, R. M., and Ellison, E. H.: Primary Peptic Ulceration of the Jejunum Associated with Islet Cell Tumor of the Pancreas, *Ann Surg* 142:709, 1955.
- Zollinger, R. M., and Elliot, D. W.: Pancreatic Endocrine Function and Peptic Ulceration, *Gastroenterology* 37:401, 1959.
- Brunschwig, A.: Results of Pancreatoduodenectomy, *Cancer* 2:763, 1949.
- Bartholomew, L. G., Baggenstoss, A. H., Morlock, C. G., and Comfort, M. D.: Primary Atrophy and Lipomatosis of the Pancreas, *Gastroenterology* 36:563, 1959.

- Charles, B., and Cochrane, W. A.: Islet Cell Tumor of the Pancreas with Chronic Diarrhea and Hypokalemia, a Recently Recognized Syndrome, *Canad Med Ass J* 82:579, 1960.
- Wermer, P.: Genetic Aspects of Adenomatosis of Endocrine Glands, *Amer J Med* 16:363, 1954.

Received for publication November 21, 1968

Ineffectiveness of Diazepam as an Antiarrhythmic Agent*

MICHAEL A. NEVINS, M.D., LEONARD M. MATTES, M.D., RUTH C. SPRITZER, M.D., ARTHUR C. WEISENSEEL, M.D., EPHRAIM DONOSO, M.D., AND CHARLES K. FRIEDBERG, M.D.

Intravenous diazepam (Valium®) has been effectively employed both as an anticonvulsant (6, 8), and as a sedative-hypnotic prior to electrocardioversion (5, 9). In one report, fewer ventricular premature systoles were noted both before and after electrical shock than with the use of sodium pentothal premedication (4). The purpose of the present study was to determine whether diazepam, like other anticonvulsants (2), has an antiarrhythmic property. The method employed was to study the drug's effect on digitalis-induced ventricular tachycardia (VT) in otherwise healthy dogs.

Method

Seventeen mongrel dogs weighing 17 to 23 kilograms were anesthetized with a mixture of chloralose and urethane. An electrocardiogram of standard lead II was continuously recorded. An initial dose of 7.5 mcg/kg of ouabain was given intravenously, immediately followed by an infusion of ouabain at a rate of 2.5 mcg/kg/min. The infusion was discontinued when the first ventricular premature systole (VPS) occurred. When VT developed, the dog was observed for five additional minutes to insure that the rhythm was stable. The test animals were then given either 0.25, 0.50, or 1.0 mg/kg of diazepam rapidly intravenously. The initial dose of diazepam was repeated (except in dogs 3, 8, and 9—see Table 1) at ten minute intervals for a maximum of five injections, depending upon the resulting cardiac rhythm. The animals were observed for any alterations in depth or rate of respiration, as well as for changes in rhythm. The experiment was terminated after an observation period of one hour.

Results

Three dogs died when the infusion of ouabain was continued after the first VPS's. These animals did not receive diazepam, and VPS's were followed in order by VT, ventricular fibrillation, and death. In the remaining dogs the infusion was discontinued at the first appearance of VPS's, and in each case stable VT occurred within 15 minutes.

Four dogs were used as controls and did not receive diazepam. In these the ouabain-induced VT persisted for 30 to 45 minutes before gradually reverting to a supraventricular mechanism with frequent VPS's, and then to regular sinus rhythm. All of these control dogs survived.

The remaining dogs received diazepam after VT was induced (Table 1).

From the Division of Cardiology, Department of Medicine, the Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

* Supported in part by U.S.P.H.S., Grants No. HE 09416-03, and No. HE 5240-08.

TABLE I

Dog	Weight (kilos)	Doses of Diazepam* (mg/kg)	Results
1	17	0.25×3	No change in basic rhythm
2	20	0.25×2	Sudden asystole seven minutes after second dose
3	19	$0.50, 0.25 \times 2$	Five minutes after second dose complete heart block with VT. Regular sinus rhythm (RSR) two minutes after third dose followed by runs of VT
4	20	0.50×5	Sinus arrest with idioventricular rhythm and bigeminy five minutes after first dose. VT restored after external massage. No change with four subsequent doses
5	23	0.50×5	RSR alternating with VT six minutes after first dose. After each additional dose there was a transient decrease in frequency of VT
6	20	0.50×5	No change in basic rhythm
7	17	0.50×5	QRS narrowed five minutes after first dose but atrioventricular dissociation, rate 140/min, persisted. Four more doses failed to alter this rhythm
8	22	0.50×1	Supraventricular tachycardia, rate 200/min, one minute after first dose. Runs VT after two minutes. RSR and multifocal VPS's after four minutes, and VT after six minutes. VF, then asystole at seven minutes
9	21	1.0×1	RSR with frequent VPS's after four minutes, then sinus bradycardia, rate 20/min, at six minutes, and asystole at seven minutes
10	23	1.0×3	More frequent sinus captures six minutes after first dose. RSR with multifocal VPS's one minute after second dose. No change after third dose

* Injections were administered at ten minute intervals

Three dogs died. Electrocardiographic changes preceded any alterations in the depth and rate of respirations. In one, VT converted to sinus rhythm with frequent VPS's three minutes after a single dose of 1.0 mg/kg of diazepam. This was followed by progressive bradycardia to a rate of 20 beats per minute and bigeminy; then by sinus arrest and asystole six minutes after the injection (Fig. 1). In a second dog the VT converted to supraventricular tachycardia, rate of 200 beats per minute, one minute after a single dose of 0.5 mg/kg of diazepam. After two minutes there were runs of VT alternating

with sinus beats and frequent multifocal VPS's. After six minutes, VT occurred followed by ventricular fibrillation and death (Fig. 2). The third dog abruptly developed asystole seven minutes after the second injection of 0.25 mg/kg of diazepam.

Of the seven surviving animals, one developed an idioventricular rhythm with bigeminy five minutes after a dose of 0.5 mg/kg diazepam. After one minute this changed to asystole lasting ten seconds before external massage restored VT. Four subsequent injections of diazepam totaling 2.0 mg/kg failed to alter the VT.

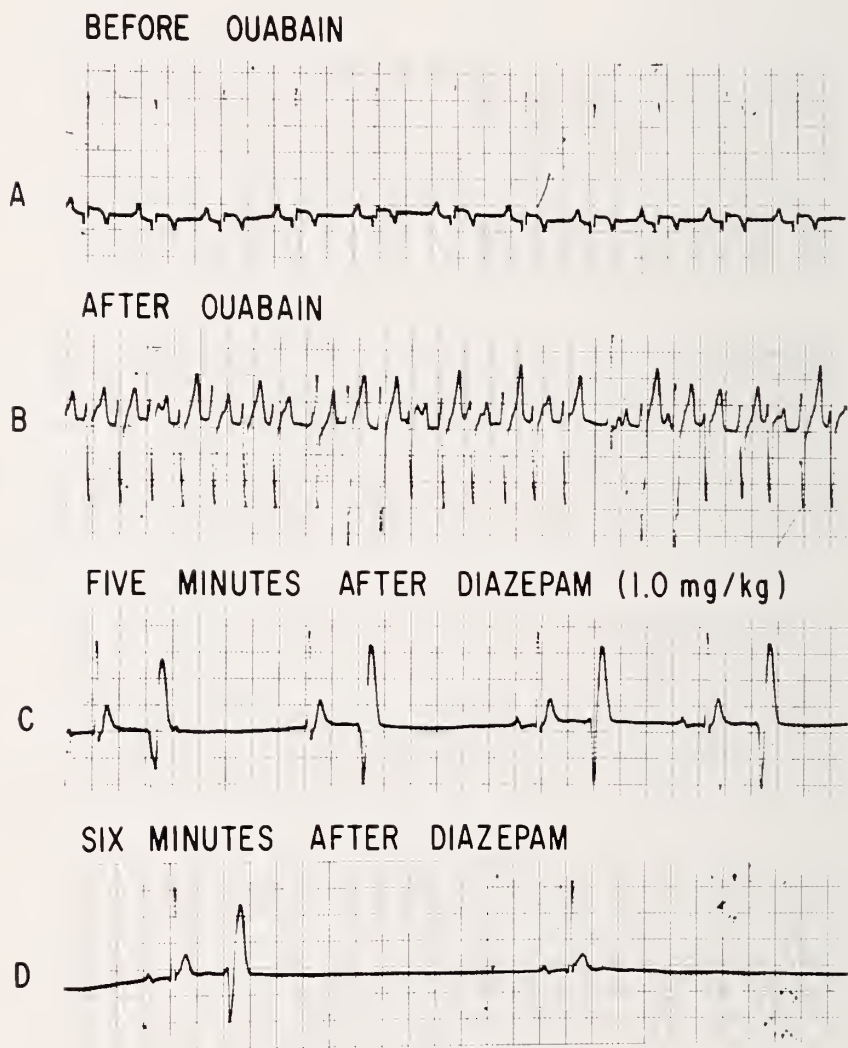


FIG. 1. Dog #9: A. Normal sinus rhythm; B. Ouabain-induced ventricular tachycardia; C. Sinus bradycardia with ventricular bigeminy and nodal escape five minutes after diazepam, 1 mg/kg; D. Progressive bradycardia and asystole one minute later.

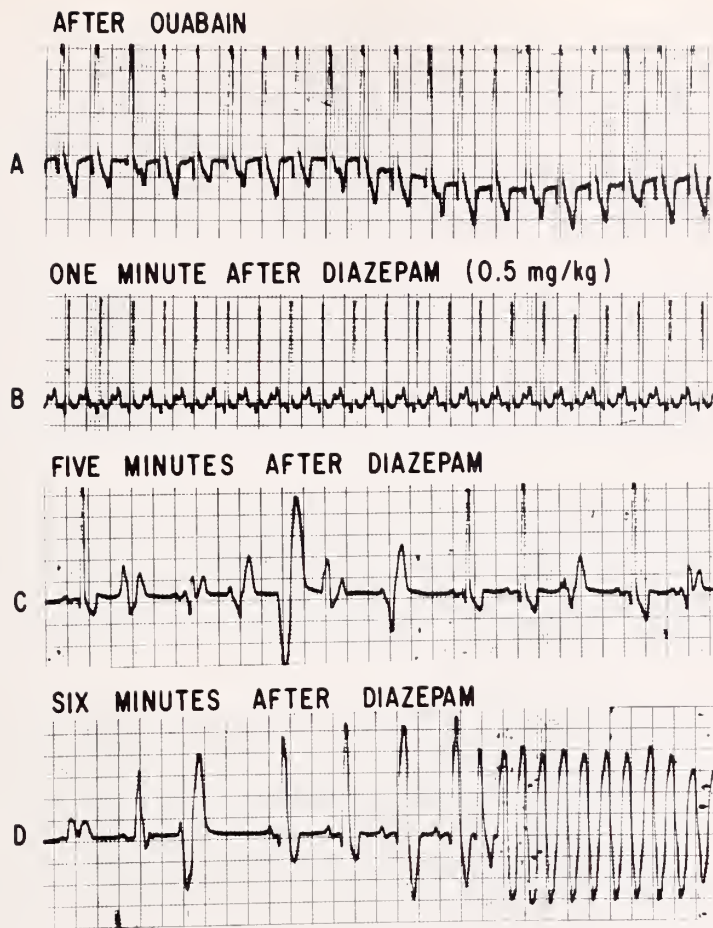


FIG. 2. Dog #8: A. Ouabain-induced ventricular tachycardia; B. Supraventricular tachycardia one minute after 0.5 mg/kg diazepam; C. Occasional sinus captures and frequent multifocal ventricular premature systoles after five minutes; D. Ventricular flutter after six minutes. This evolved into ventricular fibrillation.

In the six remaining dogs results varied. Two animals had no demonstrable response despite total doses of 0.5 mg/kg of diazepam in one and 2.5 mg/kg in the other. They remained in VT throughout the entire experiment. More frequent sinus captures appeared in three dogs within six minutes of either the first or second injection. These were associated with frequent VPS's or short runs of VT, and in no case was regular sinus rhythm without extra systoles entirely restored. In one dog the rhythm changed from VT to atrioventricular dissociation, ventricular rate 140 beats per minute, with a narrow QRS complex within five minutes of the initial injection of 0.5 mg/kg of diazepam. Four subsequent doses totaling 2.0 mg/kg, however, failed to alter this rhythm.

Discussion

Previous experiments in animals with normal sinus rhythm have indicated that diazepam has only minimal and transient hemodynamic effects (7). Dogs given increments of 1, 2, 4 and 8 mg/kg, for a total dose of 15 mg/kg over three hours, had a fall of systemic blood pressure of about 24 mm Hg, and a reduction in average heart rate from 158 beats per minute to 111 beats per minute. No significant respiratory or electrocardiographic effects were noted. Similar results were obtained in another study, in which smaller doses of diazepam were administered in cats (1). Clinical studies to date have emphasized the safety of parenteral diazepam when used in doses of 5–20 mg for the control of seizures (8), or as an anesthetic (3). No significant changes in blood pressure, heart rate, electrocardiogram, or respiratory rate were observed in this dosage range. There have been two reports of asystole associated with the administration of diazepam. In one, 11 mg of diazepam was given intravenously to a patient with a seizure disorder (6). Cardiac arrest occurred ten minutes after the injection, but death could not clearly be attributed to diazepam, since the patient had also taken large doses of phenothiazines and other drugs. Another patient had postelectrocardioversion asystole after premedication with intravenous diazepam (20 mg) (9). This complication has also been described in patients who have been shocked but have not received diazepam.

In this study intravenous diazepam appeared to modify digitalis-induced VT in eight out of ten dogs. However, the total doses employed of 0.5 mg/kg to 3.0 mg/kg were larger than those usually recommended for clinical use. Studies in our laboratory with doses of less than 0.25 mg/kg in three dogs, failed to cause any alteration of digitalis-induced VT.

An effort was made to differentiate between changes of rhythm due to diazepam, and those due to the evolution of the digitalis-induced arrhythmia. Control studies indicated that if no diazepam was administered, digitalis-induced ventricular tachycardia persisted for 30 to 45 minutes. Changes of the basic rhythm that occurred shortly after the injection of diazepam were therefore presumed to be acute responses to the drug. In addition, electrocardiographic changes preceded apparent alterations of respiration. Other investigators, using a similar technique in dogs, have demonstrated that diphenylhydantoin rapidly and consistently converts digitalis-induced VT to normal sinus rhythm.

The following comments are based on our observations: (1) The effects of intravenous diazepam on digitalis-induced ventricular tachycardia were variable. Regular sinus rhythm was not completely restored in any case, although more frequent sinus captures were noted in five out of ten animals. In three of these, however, frequent VPS's or runs of VT persisted; (2) Whereas there were no clear-cut beneficial responses, some dogs seemed to have serious drug-related side effects. Fatal arrhythmias occurred in two dogs within minutes of administration of diazepam. Sinus bradycardia developed in one animal and terminated in fatal asystole within six minutes of a single dose

of 1.0 mg/kg. In another dog, sinus arrest occurred within five minutes of an injection of 0.5 mg/kg, and was followed by idioventricular rhythm with bigeminy, and later by asystole. Following external cardiac massage, VT was restored and four additional doses of diazepam failed to alter this rhythm; (3) Doses of diazepam employed in this study were larger than those generally recommended for clinical use. Nevertheless, individual responses did not clearly correlate with the total dosage employed. Thus, fatal arrest occurred in one dog with as little as two doses of 0.25 mg/kg, whereas another dog tolerated a total of 2.5 mg/kg without any alteration of the basic ventricular tachycardia.

Summary

The effect of intravenous diazepam on digitalis-induced ventricular tachycardia was studied in ten dogs. In no case was sinus rhythm entirely restored. Three dogs died, two within seven minutes of a single dose, 0.5–1.0 mg/kg, and the other after two injections totaling 0.5 mg/kg. The mechanism of death seemed to be cardiac rather than respiratory. Of the seven surviving dogs, one developed sinus arrest within five minutes of a dose of 0.5 mg/kg, but survived after cardiac massage restored ventricular tachycardia. The remaining dogs either were not affected by repeated doses of diazepam, or had more frequent sinus capture beats associated with frequent multifocal VPS's.

The present study indicates that although intravenous diazepam may have a modifying effect on certain cardiac arrhythmias, the antiarrhythmic activity is not as potent as that of other anticonvulsants, notably diphenylhydantoin. Doses employed in this experiment (0.25–1.0 mg/kg) were relatively large, yet in no animal was sinus rhythm restored. On the other hand, serious arrhythmias developed in four of ten dogs shortly after drug administration.

Acknowledgment

We wish to thank Miss Maureen Baker for her technical assistance.

References

1. Chai, C. Y., and Wang, S. C.: Cardiovascular Actions of Diazepam in the Cat, *J Pharmacol Exp Ther* 154(2):271–280, 1966.
2. Helfant, R. H., Scherlag, B. J., and Damato, A. N.: The Electrophysiological Properties of Diphenylhydantoin Sodium as Compared to Procaine Amide in the Normal and Digitalis-Intoxicated Heart, *Circulation* 36:108–118, 1967.
3. McClish, A.: Diazepam as an Intravenous Induction Agent for General Anesthesia, *Canad Anaesth Soc J* 13:562–575, 1966.
4. Muenster, J. J., Rosenberg, M. S., Carleton, R. A., and Graettinger, J. S.: Comparison Between Diazepam and Sodium Pentothal During DC Countershock, *JAMA* 199:758–760, 1967.
5. Nutter, D. O., and Massumi, R. A.: Diazepam in Cardioversion, *New Eng J Med* 273: 650–651, 1965.
6. Prensky, A. L., Raff, M. C., Moore, M. J., and Schwab, R. S.: Intravenous Diazepam in the Treatment of Prolonged Seizure Activity, *New Eng J Med* 276:779–784, 1967.

7. Randall, L. O., Heise, G. A., Schallek, W., Bagdon, R. L., Banziger, R., Boris, A., Moe, R. A., and Abrams, W. B.: Pharmacological Clinical Studies on Valium, New Psychotherapeutic Agent of Benzodiazepine Class, *Curr Ther Res* 3:405-425, 1961.
8. Sawyer, G. T., Webster, D. D., and Schut, L. J.: Treatment of Uncontrolled Seizure Activity with Diazepam, *JAMA* 203:913-918, 1968.
9. Winters, W. L., McDonough, M. T., Hafter, J., and Dietz, R.: Diazepam: A Useful Hypnotic Drug for Direct-Current Cardioversion, *JAMA* 204:926-928, 1968.

Received for publication April 23, 1969

CLINICO-PATHOLOGICAL CONFERENCE

Anemia, Azotemia, and Rectal Bleeding in a Middle-Aged Female

Edited by

FRANKLIN M. KLION, M.D.

A 54-year-old white female was admitted to The Mount Sinai Hospital because of weakness and rectal bleeding. She was anemic for many years and received multiple vitamin preparations and liver injections with no improvement. One year earlier, a "bleeding work up" was performed because of excessive bleeding after a dental cleaning. Two months prior to entry, she developed abdominal cramps and bloody diarrhea. A urine examination one month later contained "pus" and she was treated with antibiotics. Because of severe nausea, weakness, and diarrhea all medications except vitamins were discontinued, although pyuria persisted. On the day of admission, purpuric lesions were noted on her arms and fresh blood was found on rectal examination. At age 19, she had received treatment for hyperthyroidism and exophthalmos.

She was pale and appeared chronically ill. The blood pressure was 150/65, pulse 64/minute, and respirations 18/minute. The skin was thick and dry. Purpuric lesions were present over the right forearm and cheek. The left lobe of the thyroid was enlarged and nodular. The heart and lungs were normal. A firm edge of the liver was palpated five fingerbreadths below the right costal margin, and the spleen was enlarged and felt one fingerbreadth below the left costal margin. The neurologic examination was normal. The hemoglobin was 4.3 gm%, hematocrit 14%, and erythrocyte sedimentation rate 46 mm/hour. The reticulocyte count was 7%, and platelet count 322,000/mm³. The white blood count was 6,300/mm³, with 60% segmented leukocytes, 3% band forms, 25% lymphocytes, 4% eosinophils, and 8% monocytes. The bleeding, clotting, and prothrombin time was normal. The urine specific gravity was 1.016. There was moderate proteinuria and the urinary sediment contained 3-6 red blood cells; 25-30 white blood cells had an occasional granular cast per high power field. Electrophoresis of the urine contained no protein. The blood sugar was 76 mg%, blood urea nitrogen 92 mg%, and creatinine 11.7 mg%. Electrophoresis of the serum was normal. A Coombs' test was negative. The Bromsulfalein retention was 14.5%, and the serum alkaline phosphatase activity 48.6 King-Armstrong units. The serum bilirubin, cholesterol, and SGOT were normal. Several stools were guaiac positive. A protein bound iodine determination was 17%.

After two units of whole blood the hemoglobin was 7.9 gm%. She continued to pass 2-3 semiformal stools mixed with blood and mucus. Further transfusions were given. A sigmoidoscopic examination was normal. A barium

enema examination showed a polyp of the sigmoid colon and abnormal colonic motility without evidence of obstruction, shortening, or mucosal abnormalities. The bone marrow was normocellular with slight erythroid hyperplasia, and increased number of lymphocytes and plasma cells, several in clusters with double nuclei. Stains for amyloid were negative. Compazine® and intravenous fluids were required for severe nausea, and additional blood transfusions were required because of persistent rectal bleeding.

On the 19th hospital day, the hemoglobin was 8.7 gm%, the blood urea nitrogen 43 mg%, serum creatinine 9.7 mg%, calcium 10 mg%, phosphorus 7.6 mg%, and carbon dioxide 10.2 mEq L. A radioactive iodine uptake was reported as 15% in 24 hours, and 12.5 mg/day of triiodothyronine was instituted.

Her condition remained unchanged. On the 26th day she was found comatose. The blood pressure was 200/100; pulse 76/minute and regular. The left pupil was smaller than the right, and no corneal or tendon reflexes were elicited. A spinal fluid examination prior to death was grossly bloody.

*Dr. M. Rosenthal**: Although this 54-year-old woman was hospitalized because of weakness and rectal bleeding, she had a long history of anemia which was treated in a shotgun fashion with multiple vitamin preparations and liver injections. One year before admission, she was investigated for bleeding following a dental cleaning. Hemorrhagic diatheses frequently occur after minor dental procedures, and especially after dental extractions which are particularly traumatic. It is interesting that patients with coagulation disorders may not bleed after inguinal herniorrhaphies, but bleed excessively following dental extractions. Therefore, when a patient bleeds following a dental procedure, especially when a transfusion is required, a thorough investigation for a possible coagulation disorder should be carried out.

Subsequently she developed abdominal cramps and diarrhea, and then nausea and weakness. I assume her physician suspected that some of her symptoms were related to drug therapy, since all medications except vitamins were discontinued. On the day of admission, she developed purpura and rectal bleeding. She was treated for hyperthyroidism and exophthalmos many years before, and although the nature of the treatment was not known, we can assume she received Lugol's solution.

On examination, she was pale and her skin was thick and dry. Purpura was present over the right forearm and cheek. The appearance and distribution of purpura may be helpful in diagnosis. With cachexia or senility, the purpuric lesions have a peculiar violaceous hue, and are usually found over the forearms and wrists. In defibrination states or hypofibrinogenemia, the purpura is extensive and frequently may be generalized. Purpura seen with thrombocytopenia has a petechial component, and commonly is associated with gingival bleeding.

Anemia, with a possible bleeding diathesis and hepatosplenomegaly, sug-

* Associate Clinical Professor of Medicine, the Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

gests lymphoma, some form of hypersplenism, or a hemolytic anemia. The laboratory findings, unfortunately, are not very helpful in establishing a diagnosis. The sedimentation rate was only mildly elevated considering she was very anemic. The normal platelet count, however, excludes hypersplenism or thrombocytopenia that may be associated with an infiltrated marrow. The reticulocyte count of 7 percent suggests hemolysis, since patients who bleed even massively rarely have reticulocyte counts exceeding 2 or 3 percent. Why this occurs is not known. Therefore, we have some indirect evidence that even though she was losing blood, hemolysis also may have been present. The bleeding and clotting were normal, and the prothrombin time, which might have been prolonged if she had extensive infiltrative disease of the liver, was also normal.

Electrophoresis of the urine contained no protein, although protein was found in a casual specimen. Electrophoresis of the serum did not show an abnormal globulin spike. If an abnormal serum globulin had been found, rectal bleeding and hepatosplenomegaly with a nonthrombocytopenic purpura and long-standing anemia would be typical of the dysproteinemias, such as multiple myeloma or Waldenstrom's macroglobulinemia. Certainly, in macroglobulinemia, I would have expected an abnormal gamma spike, or a homogenous abnormal macroglobulin. In multiple myeloma, a protein abnormality, either in the serum or in the urine, can be expected in about 95 percent of the patients, but may be missed with paper electrophoresis.

The negative Coombs' test simply indicated that she did not have an autoimmune type of hemolytic anemia, but it did not exclude other types of hemolysis. The protein bound iodine was very low, confirming the initial clinical impression that the patient had myxedema.

She continued to have diarrhea and a polyp was found in the colon. The polyp may have been responsible for the rectal bleeding. On the other hand, if the rectal bleeding and purpura are related, a systemic cause must be considered.

Finally, the bone marrow showed an increased number of lymphocytes and plasma cells in clusters, and double nuclei. The plasma cells were morphologically normal. In multiple myeloma, the plasma cells may sometimes appear very close to the normal, and significant number of patients with multiple myeloma, perhaps 10 to 15 percent, present with anemia, azotemia, and rectal bleeding without bone pain. Why do patients with multiple myeloma or Waldenstrom's macroglobulinemia bleed? A number of them have a deficiency of factor II or V. Bleeding, however, is usually due to the presence of an abnormal protein that somehow interferes with the conversion of fibrinogen to fibrin. Some patients with multiple myeloma have a bleeding diathesis in association with primary amyloidosis. A routine investigation for the usual causes of bleeding in these circumstances may be normal. The bleeding diathesis in primary amyloidosis is quite characteristic. The purpura is periorbital and periauricular. Routine coagulation tests are also normal. It has been proposed that amyloid infiltration of the small blood vessels leads to the

extravasation of blood; practically all of the patients with amyloidosis and this type of bleeding diathesis have multiple myeloma at autopsy.

I shall not discuss the relationship between amyloidosis and multiple myeloma, but would like to consider those aspects of her disease which would be compatible with amyloidosis, rather than multiple myeloma alone. She had azotemia and hepatosplenomegaly, and although approximately 20 percent of patients with multiple myeloma have palpable spleens, very large splenomegaly is unusual. Amyloidosis would also explain the elevated alkaline phosphatase activity and BSP retention. Therefore, primary amyloidosis, or amyloidosis in association with multiple myeloma, may explain her symptom complex.

Two conditions that frequently are difficult to separate are multiple myeloma and Waldenstrom's macroglobulinemia. Both can manifest themselves as only a long-standing anemia. Both of them are basically dysproteinemias so that rectal, nasal, or gastrointestinal bleeding and azotemia are a feature of some cases of myeloma, and many cases of Waldenstrom's macroglobulinemia. Renal failure is unusual with Waldenstrom's, and much more common in multiple myeloma. Purpura is more frequently seen with multiple myeloma than it is with Waldenstrom's, but such a differentiation is tenuous.

The bone marrow in Waldenstrom's macroglobulinemia shows a spectrum from very peculiar small lymphocytes, to plasmacytic lymphocytes. In reviewing this patient's marrow, transitional plasma cells were seen in fields in which there was an extensive infiltration with lymphocytes. Did this lady have multiple myeloma with amyloidosis, or Waldenstrom's macroglobulinemia, or did she have a sarcoma with a dysproteinemia? Based mainly on the bone marrow findings, I think the patient had a form of Waldenstrom's disease. In other words, she had that peculiar type of lymphomatous, or lymphocytic proliferative disease associated with dysproteinemia that has a characteristic group of symptoms, namely a refractory, long-standing anemia, a bleeding diathesis, and hepatosplenomegaly.

*Dr. B. Rybak**: At autopsy she had confluent purpuric lesions on the arms and cheeks, and 2,000 cc of straw-colored fluid was found in the abdomen.

The liver weighed 1,600 grams. The surface was nodular. Many dark red, depressed areas over the surface were due to peripheral infarcts. On histologic examination, the portal tracts were widened by infiltration of an amorphous eosinophilic material resembling amyloid. The bile ducts were preserved (Fig. 1). The arteries were markedly deformed, and many veins were completely occluded, and probably were responsible for the infarcted areas of the parenchyma. Metachromatic and Congo red stains confirmed the presence of amyloid. Occasionally, multinucleated foreign body giant cells were seen adjacent to the amyloid.

The spleen weighed 150 grams. It was firm and the capsule was wrinkled. The follicular pattern was obliterated, and the large vessels infiltrated by

* Fellow, Department of Pathology, The Mount Sinai Hospital, New York, N.Y. 10029.

amyloid (Fig. 2). The lymph nodes and adrenal glands also contained deposits of amyloid.

Each of the kidneys weighed 210 grams. They were pale in color and the surface was smooth. Some of the intralobular vessels and the mesangium of the glomeruli were involved by deposition of amyloid. The Bowman's spaces and renal tubules were distended by a proteinaceous material (Fig. 3), and there was marked interstitial fibrosis and clusters of lymphocytes and an occasional segmented neutrophil typical of pyelonephritis. Many leukocytes also were found in the renal tubules (Fig. 4).

The thyroid gland showed a chronic thyroiditis with fibrosis, infiltration of lymphocytes, and atrophy of the acini (Fig. 5). The parathyroid glands were normal.

The bone marrow was hyperplastic with areas of lymphocytic infiltration.

This patient had hypothyroidism and primary amyloidosis involving liver, spleen, adrenals, pancreas, myocardium, and the lymph nodes. She bled from a large ulcerated adenomatous polyp in the sigmoid colon, and died of an extensive intracerebral hemorrhage which ruptured into the third ventricle. It is of some interest that thyroidectomy or thyrotropin administration to animals can produce primary amyloidosis.

In 1966, Symmers reported three patients with hypothyroidism and generalized amyloidosis. In two patients total thyroidectomy had been performed. The third case was a young man who received an inadvertent overdose of I^{131} . Two years later he developed severe hypothyroidism, anemia, hepatosplenomegaly, a very large tongue, and generalized lymphadenopathy. A

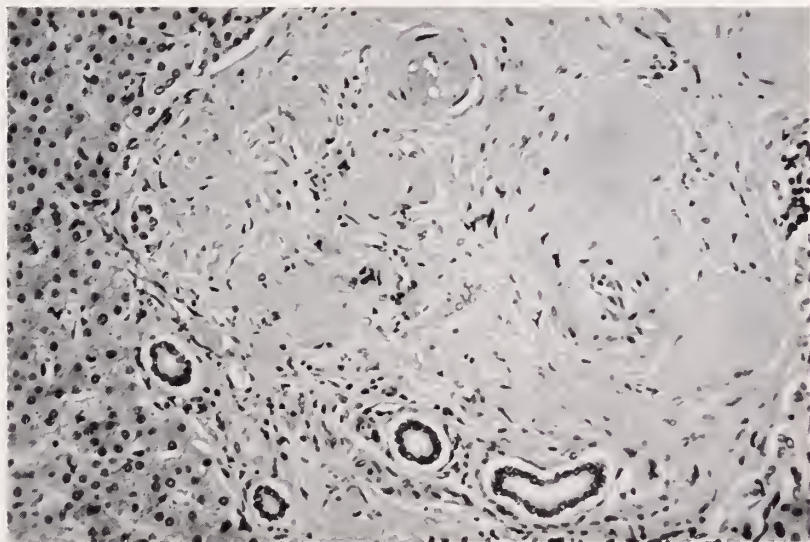


FIG. 1. Portal tract of the liver involved by amyloid. The lumens of the artery and vein are narrowed (H & E $\times 400$).

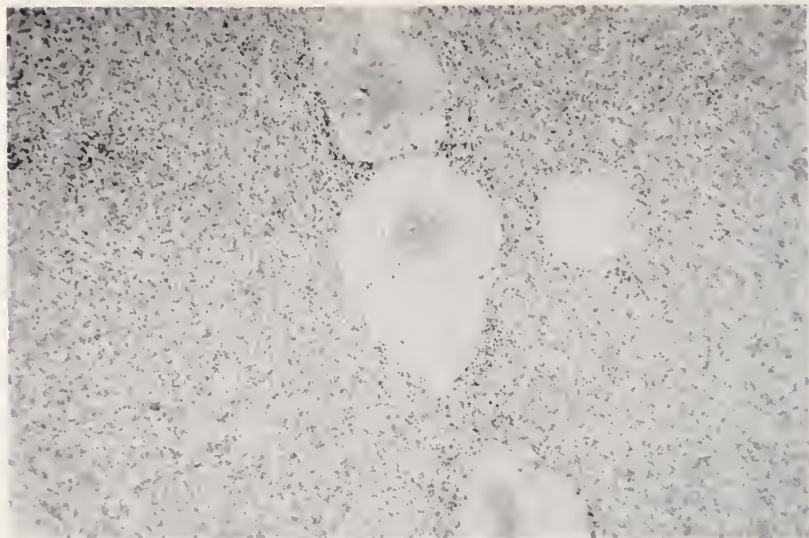


FIG. 2. Spleen showing perivascular deposition of amyloid (H & E $\times 100$).

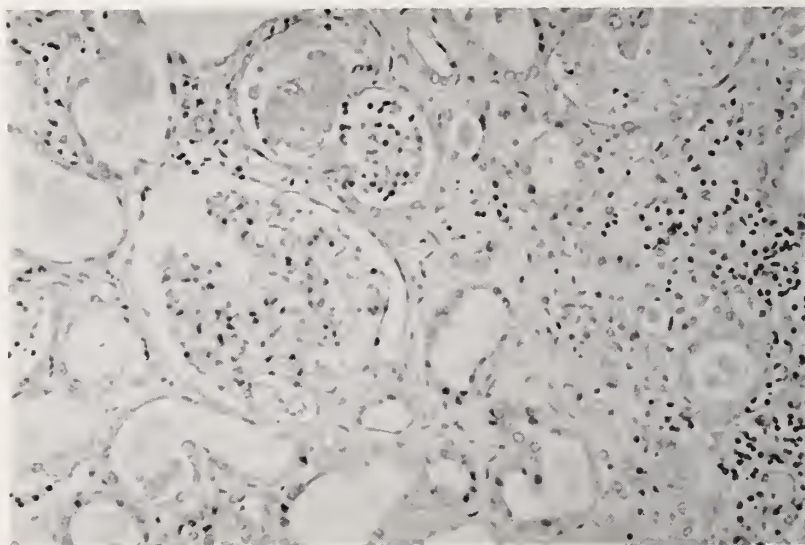


FIG. 3. Kidney showing interstitial fibrosis and infiltration of mononuclear cells. The tubules are atrophic and dilated, and contain proteinaceous material. Polymorphonuclear leucocytes are seen within the tubules (H & E $\times 100$).

biopsy of one of the lymph nodes revealed amyloid. After six months of replacement thyroid therapy, his spleen, liver, lymph nodes, and tongue regressed in size. This case also suggests a relation between hypothyroidism and primary amyloidosis.

Dr. Rosenthal: Can you explain the lymphocytic infiltration of the bone marrow?

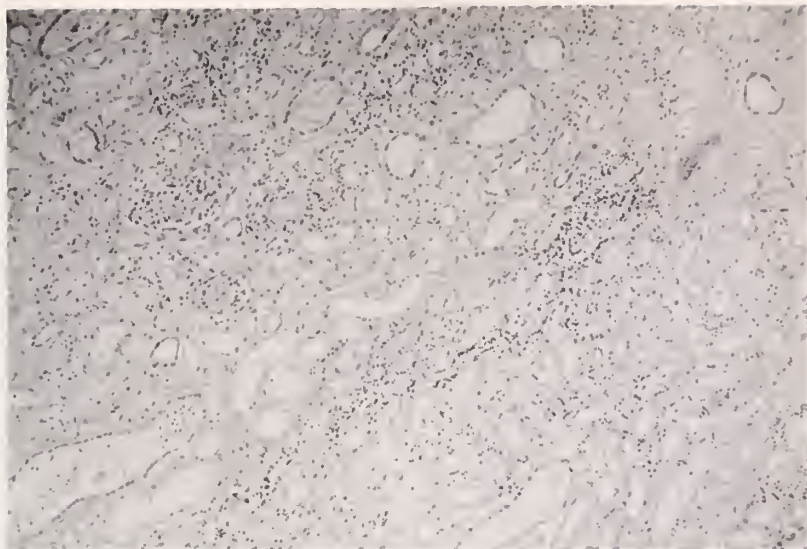


FIG. 4. Renal medulla showing atrophic collecting ducts, interstitial fibrosis, and a mononuclear cell infiltration (H & E $\times 40$).

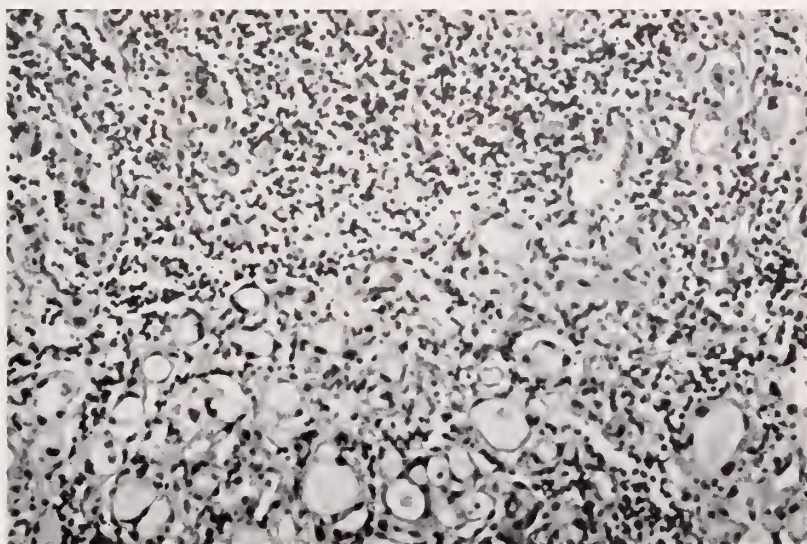


FIG. 5. Lymphocytic reaction and interstitial fibrosis in the thyroid. The acini are atrophic (H & E $\times 100$).

Dr. Rybak: No.

Dr. Rosenthal: This, of course, raises the question as to why the patient developed primary amyloidosis.

Dr. H. Popper:* I frequently cannot distinguish between amyloidosis with reactive plasmacytosis of the marrow and multiple myeloma and amyloidosis.

* Professor and Chairman, Department of Pathology, the Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Dr. Rosenthal: Routine electrophoretic patterns of serum and urine sometimes are normal, while immunoelectrophoresis may reveal an abnormal globulin and enable one to make a diagnosis. Usually the electrophoretic pattern, in addition to plasma cytosis, may permit the distinction between multiple myeloma and reactive hyperplasia.

Final Diagnosis:

PRIMARY AMYLOIDOSIS INVOLVING THE LIVER, SPLEEN, KIDNEYS, LYMPH NODES,
AND ADRENAL GLANDS.

CHRONIC THYROIDITIS.

CHRONIC PYELONEPHRITIS.

ADENOMATOUS POLYP OF THE SIGMOID COLON.

EXTENSIVE INTRACEREBRAL HEMORRHAGE, WITH RUPTURE INTO THE THIRD
VENTRICLE.

References

Symmers, W. St. C.: Primary Amyloidosis: A Review, *J Clin Path* 9:187-211, 1956.

Symmers, W. St. C.: Five Cases of Primary Generalized Amyloidosis and some other Unusual Cases, *J Clin Path* 9:212-228, 1956.

Received for publication May 2, 1969

RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., Co-Editors

CASE NO. 332

A 30-year-old female was admitted to the hospital for investigation of complaints of right lower quadrant pain and frequency of urination. Urinary frequency had been present for many months, and intermittent right lower quadrant and deep pelvic pain had occurred during the past few weeks. General physical examination revealed no abnormality. Pelvic examination revealed a large soft mass.

Radiologic examination demonstrated a large 13 cm rounded lucent mass occupying most of the pelvis. The mass was sharply margined and perfectly smooth in outline. Intravenous pyelography showed the mass to indent the bladder moderately on its superior aspect (Fig. 1). There was a 1.5 cm



Case 332, Fig. 1. Abdominal radiograph from an intravenous pyelogram made 15 minutes after injection shows opaque material in both pelvic ureters and bladder. A 13 cm round lucent sharply margined mass is seen in the pelvis (arrows). There is no effect on the ureters. The mass indents the superior contour of the bladder. There is a tooth-like structure along the superior margin of the mass (arrow A).



Case 332, Fig. 2. Abdominal radiograph from a pelvimetry examination made five years previously, demonstrates tooth-like structures in the right midabdomen overlying the fetal rib cage (arrows). There is no associated lucent shadow. The fetal structures otherwise show no unusual feature; there is molding of the fetal head.

structure which resembled a tooth along the superior margin of the mass. The ureters in the pelvis were undisturbed. An erect film failed to show a fluid level. Barium enema and GI series were also performed, and revealed extrinsic pressure effects on the sigmoid colon and lower small bowel loops, but no fixation, angulation, or mucosal abnormality was present. The radiographic diagnosis of an ovarian dermoid cyst containing sebaceous material and abortive dentition was suggested.

Previous films of this patient were reviewed and an abdominal film was noted from a pelvimetry examination performed five years previously (Fig. 2). High in the right midabdomen there could be seen tooth-like structures overlying the fetal rib cage. These had gone unobserved at the time of the original examination. No associated lucency was visualized.

At laparotomy, a large dermoid cyst of the right ovary was removed uneventfully. The presence of sebaceous material and abortive dentition was confirmed by the pathologist.

Discussion

This case is presented as an interesting verification of the mobility of the ovary during pregnancy. As the gravid uterus enlarges, the adnexa rise progressively out of the pelvis. In this case, their position in the midabdomen at term is documented by the tooth-like structures seen on the original pelvimetry study performed five years previously (Fig. 2).

The most characteristic features of dermoid cyst are illustrated in this case (Fig. 1). The mass is noninfiltrative, and thus is sharply outlined when in an uncomplicated state, it is radiolucent because of its fat-containing sebaceous material, and it contains tooth-like structures which represent abortive dentition. Bilaterality, a common finding, was not present in this case. A fluid level between cyst contents of different densities (fat and soft tissue) is said to be present upon occasion; this was searched for with horizontal-ray film but was not found. Gradual enlargement over the years is indicated by the interval follow-up.—H.M.P.

Case Report: DERMOID CYST OF THE OVARY VERIFYING OVARIAN MOBILITY DURING PREGNANCY.

Acknowledgment

This case is presented through the courtesy of Dr. James Brescia, Good Samaritan Hospital, Suffern, New York.

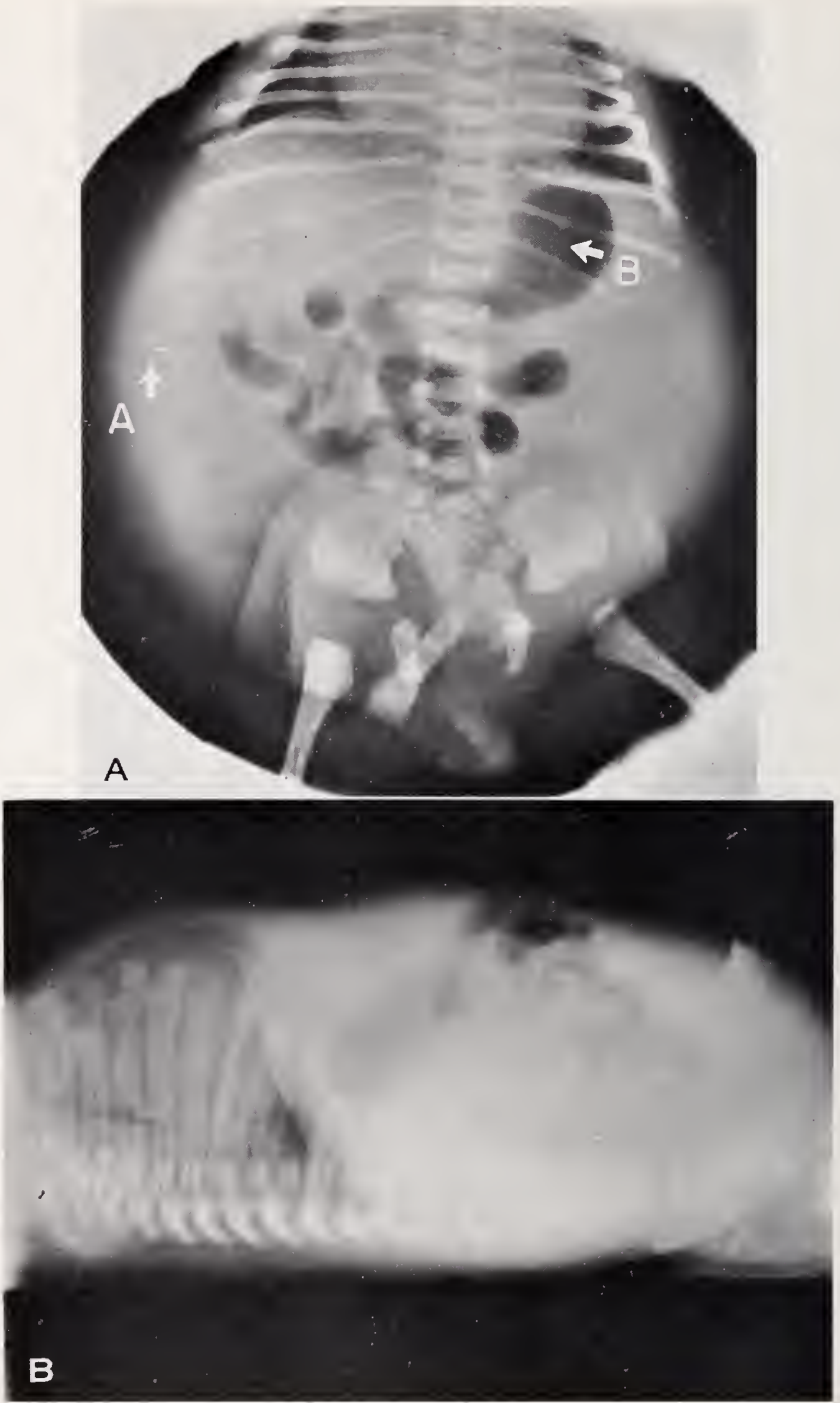
CASE NO. 333

A full-term six pound male infant was noted at birth to have marked abdominal distension. Gestation had been uneventful. Family history was noncontributory.

Clinical evaluation revealed a protuberant abdomen which was soft and doughy, suggesting ascites. No masses were palpable. Moderate respiratory distress was believed to be secondary to the distended abdomen. Radiographic studies within the first hour of life revealed bulging flanks and a few tiny abdominal calcifications (Figs. 1A and 1B). The diagnosis of meconium peritonitis was suggested.

The abdominal wall was abnormal, with peculiar thickening and corrugation of the tissues. The abdomen bulged markedly laterally in the flanks but no so anteriorly, with the baby supine. An unusual pattern of cyanosis was noted, most marked from the umbilicus downward. The testes were cryptorchid. The diagnosis of "prune-belly" or "Eagle-Barrett" syndrome was suggested; that is, the association of absent or deficient abdominal wall musculature with genitourinary abnormalities. Bilateral congenital dislocations of the hips and calcaneovalgus deformities of the feet were also noted.

The baby failed to pass urine. Paracentesis in the right midabdomen pro-



Case 333, Figs. 1A and B

duced 150 cc of clear straw-colored fluid, shown by subsequent electrolyte determinations not to be urine. Attempts to pass a urethral catheter were unsuccessful; the catheter failed to negotiate the posterior urethra. A needle was inserted suprapubically into the urinary bladder and a large quantity of urine was withdrawn. An indwelling catheter was introduced, opaque material injected, and films were obtained in multiple projections (Figs. 2A, 2B and 2C). A distended, peculiarly shaped bladder was delineated, along with markedly dilated and tortuous ureters, the latter visualized by vesicoureteral reflux bilaterally. The internal structures of the left kidney and the most superior portion of the left ureter were not dilated; the internal structures of the right kidney were not demonstrated. The bladder neck tapered in an unusual fashion, the the posterior urethra seemed cut off in an angular fashion suggesting an organic obstruction.

The BUN rose despite the suprapubic drainage. Intravenous pyelogram barely visualized the left kidney, but failed to visualize the right kidney. Bilateral loop ureterostomies were performed. At surgery, the cause for the dilated ureters was not determined. Although neither kidney was dilated, urine drained subsequently only from the left side.

The baby became severely jaundiced and septic, and expired shortly after transfer to another institution. Postmortem examination revealed a normal left kidney which was not hydronephrotic. The right kidney was described as dysplastic. There was evidence of sepsis. The posterior urethra was widened in a peculiar fashion, but no organic obstruction was defined here, nor at the ureteral transition zones as well.

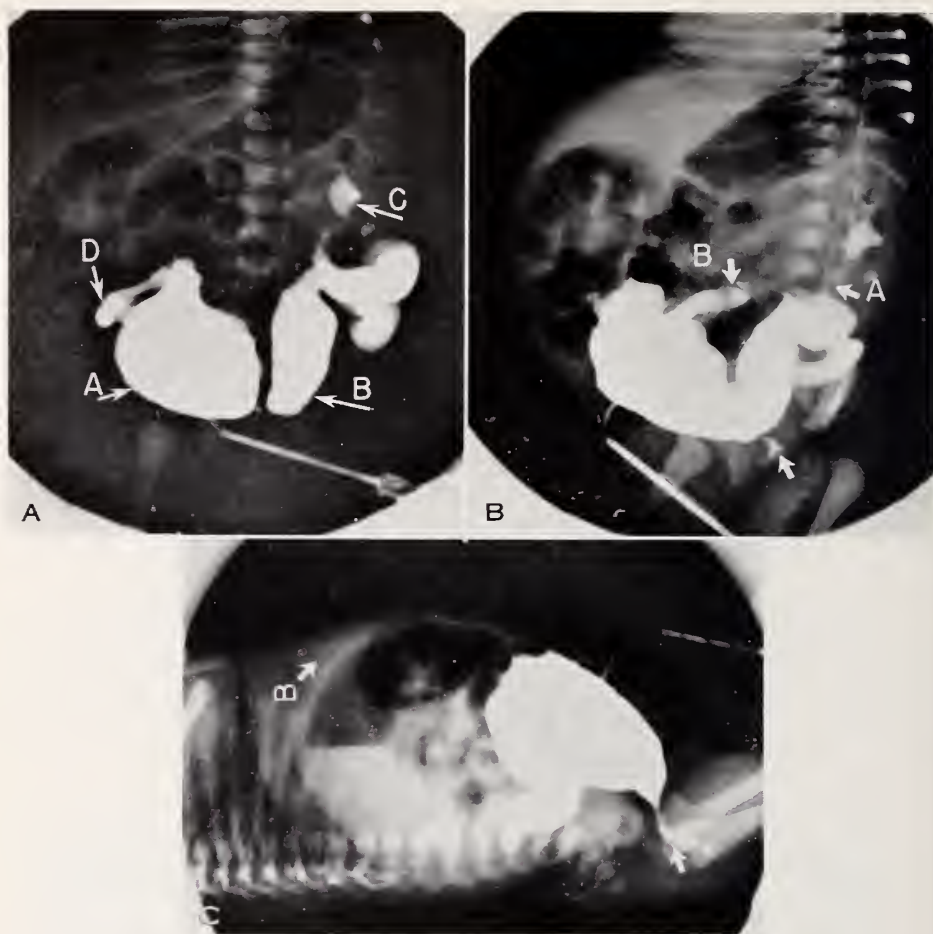
Discussion

The syndrome of absent or deficient abdominal wall musculature and genitourinary abnormalities is well documented in the literature, and re-

Case 333, Fig. 1A. Anteroposterior radiograph of the abdomen made within the first hour of life shows very marked bulging of both flanks. There is wide homogeneous soft tissue density between the skin margins and the gas-filled loops of the upper gastrointestinal tract, and no fat stripes are seen. Both these features suggest ascites. There are a few tiny calcifications in the right lateral abdomen (arrow A), and similar calcifications in the left upper quadrant overlying the gastric air shadow (arrow B). The presence of these calcifications along with the ascites lead to an erroneous diagnosis of meconium peritonitis. The nature and etiology of these calcifications was never determined.

The extent to which gas has progressed through the upper gastrointestinal tract is consistent with the short time interval since delivery. The lung bases are clear. Both hips are dislocated.

Case 333, Fig. 1B. Lateral projection of the abdomen was made with the patient supine employing cross-table technic and horizontal ray. The abdominal wall is remarkably flat, and does not bulge anteriorly as one might have expected. This marked discrepancy is due to the lack of tone in the abdominal wall and should strongly suggest the correct diagnosis. The calcifications are not further localized.



Case 333, Fig. 2A. Anteroposterior radiograph of the abdomen shows a needle connected to a thin polyethylene tube pointing to the suprapubic region, through which opaque material was introduced. Opaque material fills the bladder of peculiar shape (A), refluxes into a remarkably dilated and tortuous left ureter (B) via a peculiar uretero-vesicle junction, and ultimately delineates the internal structures of the left kidney (C) which are of normal caliber along with a small undilated segment of the upper ureter. The dilated and tortuous right ureter is also visualized by reflux (D).

Case 333, Fig. 2B. Right posterior oblique projection again demonstrates the normal caliber of the left upper tract and upper ureter, with a sharp transition to a very dilated and tortuous lower ureter (arrow A). A transition point is also seen in the upper portion of the right ureter (arrow B), but no opaque material outlines the right upper tract. The posterior urethra is also seen in this view and shows a peculiar angular cut-off (arrow).

ferred to eponymically as the "Eagle-Barrett" syndrome, after their description of the condition, or more recently as "prune-belly" syndrome, in a more graphic vein (1, 2). The appearance of the abdominal wall is characteristic: the skin is wrinkled, corrugated, and criss-crossed with creases, while the wall itself is lax and thin. Thus the similarity to the surface pattern of a dried prune is obvious.

Virtually all of the cases reported have occurred in males. Although abnormalities in other organ systems are frequently present, the genito-urinary findings are constant, characteristic, and severe. The bladder and ureters are atonic and functionally ineffective, with distension and tortuosity. The kidneys may be hydronephrotic or dysgenetic. Some form of urethral outlet obstruction is apparently often present, but whether this is caused by a valve, an anomalous posterior urethra, or an abnormal bladder neck is most often not clearly established, as in this case. The testes are always cryptorchid.

Of course, treatment must be directed initially toward the establishment of effective drainage of the urinary tracts to conserve all functioning renal tissue. However, drainage is usually poor and difficult to establish, indicating that an intrinsic disease of smooth muscle is present with poor propulsive abilities. Significant reconstruction of the abdominal wall is usually not feasible. While some cases are relatively mild and are compatible with long term survival, the prognosis by and large is grim.

In the case presented, the appearance of the abdominal wall was classical, along with the status of the urinary tracts, cryptorchid testes, and associated orthopedic deformities. It is unfortunate that the exact nature of the urethral outlet obstruction remains unclarified, as does the nature of the bilateral ureteral transition zones. The cause for the abdominal calcifications, initially misleading, is likewise not elucidated. The mechanism for the production of the ascites, the dominant clinical feature initially, is also not clearly understood; it is said, however, that lower urinary tract obstruction is a well-recognized cause for neonatal ascites.

The plain film roentgen findings faithfully reflect the laxity of the abdominal wall, and should suggest the diagnosis; the flanks bulge widely but the anterior abdominal wall fails to protrude significantly, provided, that is, that gravity is employed appropriately, as in Figures 1A and 1B. This is still another application for horizontal ray technics, too often neglected in many radiographic "routines".

Case 333, Fig. 2C. Lateral projection made with cross-table technic (same as in Fig. 1B) shows the remarkable anterior redundancy of the dilated ureters and bladder. The undilated left upper tract is again noted. The bladder neck tapers in an unusual configuration, and again the posterior urethra is cut off in a sharp angular fashion (arrow). The appearance suggests some organic obstruction at this point, exact nature undetermined. One can also see faint calcifications in or near the anterior abdominal wall in the upper abdomen anterior to the gastric air shadow. These correspond to the left upper quadrant calcifications described in Fig. 1A (arrow B).

Conditions which might be confused with this one include omphalocele, and infants in uremia due to severe urethral valvular obstruction, who may have distended flabby abdomens.—H.M.P.

Case Report: "PRUNE-BELLY" SYNDROME.

Acknowledgment

This case is presented through the courtesy of Drs. Arnold Kramer and Marvin Buttermann, Good Samaritan Hospital, Suffern, New York.

References

1. Bourne, C. W., and Cerny, J. C.: Congenital Absence of Abdominal Muscles: Report of 6 Cases, *J Urol* 98:252-9, 1967.
2. Williams, D. I., and Burkholder, G. V.: The Prune Belly Syndrome, *J Urol* 98:244-51, 1967.

CASE NO. 334

A 39-year-old male was referred for gastrointestinal x-ray studies as part of a general medical check-up. No significant gastrointestinal complaints were present except for some pyrosis and mild dyspepsia. General physical examination revealed no abnormal findings. Past history revealed that the patient had had a number of upper respiratory infections within a short space of time two years previously. No trend, pattern, sequellae, or other illnesses evolved from these infections. General physical examination, routine examinations of the blood and urine, total serum protein determination, and albumin-globulin ratio were all within normal limits. The pattern of infections was attributed to coincidence, and indeed they proved to be self-limited. Past history was otherwise noncontributory.

Upper GI series, small bowel study, and barium enema examinations were performed. There was a pattern of punctate, pinhead-sized radiolucencies distributed uniformly throughout the small bowel from duodenum through ileum. The pattern of these tiny shadows was superimposed on the normal underlying fold pattern of the valvulae conniventes. No large filling defect or contour defect was seen. The bowel contracted normally and was not dilated. The loops were not abnormally separated. There were no transient intussusceptions. There were no abnormal secretions. The esophagus, stomach, duodenal bulb, and colon were normal (Figs. 1, 2, and 3).

Routine laboratory studies of the blood and urine, including 12-channel autoanalyzer battery, were normal. Serum protein evaluation included: total serum protein determination with albumin-globulin ratio; immunoglobulin electrophoresis (photographic read-out); and quantitative immunoglobulin determinations (two different laboratories). All determinations were within normal limits.

Peroral small bowel biopsy was performed, with the specimen judged to be from the midduodenum. Four tiny bits of tissue were obtained in a pattern which suggested that four of the tiny nodules had been sampled. All four



Case 334, Fig. 1. Anteroposterior abdominal radiograph from GI series shows a pattern of punctate, pinhead-sized radiolucencies distributed uniformly throughout the upper jejunal loops. The pattern of these tiny shadows is superimposed on the normal underlying fold pattern of the valvulae conniventes. No large filling defect or contour defect is seen. The bowel is contracting normally and is not dilated. The loops are not abnormally separated. The stomach and duodenal bulb are normal.



CASE 334, Fig. 2. Posteroanterior radiograph from air contrast portion of barium enema examination demonstrates excellent mucosal coating in the terminal ileal loops. Again, a pattern of punctate, pinhead-sized radiolucencies is seen. The contours of the small bowel loops are smooth. The colon is normal.

were virtually identical, and consisted of a nodule lymphoid tissue covered by normal mucosa. Six pathologists examined the slides and all reported benign lymphoid cellular structure with no indication of neoplastic features.

The patient remains asymptomatic in every respect. It is planned to examine him periodically via appropriate laboratory and radiologic parameters.—H.M.P.



Case 334, Fig. 3. Magnified view of the mucosal pattern in the jejunum.

Discussion

BY RHONA J. KELLER, M.D.

The roentgen appearance of the small bowel in nodular lymphoid hyperplasia characteristically consists of slight widening of the lumen of the bowel, the mucosa of which demonstrates innumerable small (1-3 mm), smooth, sharply circumscribed, discrete nodular defects which are superimposed on and between the normal sized mucosal folds. These nodules represent hyperplastic lymphoid follicles within the submucosa of the bowel, although very rarely they have been reported to be beneath the muscularis mucosa. Although they are distributed throughout the small bowel, the roentgen appearance is most characteristic in the jejunum.

The roentgen differential diagnosis includes sclerosing ileitis when the changes are discovered in the terminal ileum; benign lymphoma and lymphosarcoma, in which the nodules tend to be larger and more variable in size; and Whipple's disease, where the folds are usually thickened appreciably and there is a finer nodularity due to the expanded villi. Differentiation from normal small bowel folds seen on end is usually not difficult since the number of nodules far exceeds the number of folds in any segment, and one can define numerous nodules which clearly fall between the folds.

Small bowel changes in the acquired antibody deficiency syndromes, if present, are usually indistinguishable from those seen in idiopathic sprue. Small bowel roentgen changes in congenital antibody deficiency states have not yet been confirmed. Nodular lymphoid hyperplasia of the small bowel, as described in dysgammaglobulinemia type II (and in one case of isolated

IgA-type IV deficiency), represents a more specific finding and allows, with the appropriate immunoglobulin studies, a specific diagnosis. The roentgen appearance in these latter cases is indistinguishable from that seen in the case presented. With normal globulin studies, no ancillary features or abnormalities, and the histologic features of the small bowel biopsy as described, the case presented is left in the classification of benign nodular lymphoid hyperplasia of the small bowel of unknown etiology.—R.J.K.

Case Report: BENIGN NODULAR LYMPHOID HYPERPLASIA OF THE SMALL BOWEL.

Acknowledgment

This case is presented through the courtesy of Drs. Leonard Beier and Lionel Zemek, Good Samaritan Hospital, Suffern, New York.

References

- Cohen, N., Paley, D., and Janowitz, H. D.: Acquired Hypogammaglobulinemias and Sprue: Report of a Case and Review of the Literature, *J Mount Sinai Hosp NY* 28:421, 1961.
- Editorial: A Proposed Classification of Primary Immunologic Deficiencies, *Amer J Med* 45:817, 1968.
- Gryboski, J. D., Self, T. W., Clemett, A., and Herskovir, T.: Selective Immunoglobulin Deficiency and Intestinal Nodular Lymphoid Hyperplasia, *Pediatrics* 42:833, 1968.
- Hermans, P. E., Huizenga, K. A., Hoffman, H. N., Brown, A. L., and Markowitz, H.: Dysgammaglobulinemia Associated with Nodular Lymphoid Hyperplasia of the Small Intestine, *Amer J Med* 40:78, 1966.
- Huizenga, K. A., Woolaeger, E. E., Green, P. A., and McKenzie, F.: Serum Globulin Deficiencies in Non-Tropical Sprue with Report of Two Cases of Acquired Agammaglobulinemia, *Amer J Med* 31:572, 1961.
- McCarthy, C. F., Austad, W. I., and Read, A. E. A.: Hypogammaglobulinemia and Steatorrhea, *Amer J Dig Dis* 10:945, 1965.
- Pelkonen, R., Siurala, M., and Vuopio, P.: Inherited Agammaglobulinemia with Malabsorption and Marked Alterations in the Gastrointestinal Mucosa, *Acta Med Scand* 173:549, 1963.

CASE NO. 335

A five-year-old male child complaining of severe abdominal pain was admitted to the hospital with the diagnosis of anaphylactoid purpura. Following a febrile illness with an earache some days prior to admission for which oral penicillin was administered by the parent, the child developed a purpuric rash on the lower extremities along with swelling, pain, and tenderness of the knees. Acute otitis media was also present. The diagnosis of anaphylactoid purpura was made two days prior to admission. After an initial improvement, severe abdominal pain developed with vomiting and brownish-red stools. Past history and family history were noncontributory. Physical examination revealed a fading purpuric rash on the lower trunk and lower extremities, diffuse abdominal tenderness with no masses palpable, and subsiding otitis media. Routine laboratory examinations revealed no distinctive abnormality.

Plain film study revealed virtually a gasless abdomen. Multiple rounded



Case 335, Fig. 1. Anteroposterior radiograph of the abdomen made 45 minutes after the ingestion of barium reveals all of the barium to be still in the stomach. The patient had been in the right lateral recumbent and right anterior oblique positions during this time to facilitate gastric emptying. The sequence thus infers pyloric obstruction. There is a small amount of gas in the left colon, but the remainder of the colon and the entire small bowel are devoid of gas. "Pseudotumors" representing enlarged, gasless small bowel loops were seen on the original radiograph, but are difficult to appreciate in reproduction. The shadows represent enlarged small bowel loops due to bleeding into the gut wall.



Case 335, Fig. 2. Posteroanterior radiograph of the abdomen from the barium enema study shows the colon and most of the small bowel filled with barium. The filled colon appears normal. The small bowel mucosal pattern is abnormal. The folds appear thickened and somewhat stiff, having lost their normal gracile appearance. A stacked coin appearance is suggested in some areas. There are contour defects noted which suggest thumb printing.



Case 335, Fig. 3. Postevacuation study reveals the colon to be empty, but virtually the entire small bowel remains filled with barium. One can now see an exquisite demonstration of the distorted fold pattern; stacked coin appearance, thumb printing, spikey folds, and increased separation between the barium filled loops are all observed.

soft tissue shadows or "pseudotumors" were noted which represented loops of bowel apparently enlarged due to bleeding into the gut wall, rather than representing the more usual "fluid filled loops." Barium swallow was attempted. All the ingested barium was still retained in the stomach 45 minutes later, despite appropriate positioning of the patient to facilitate gastric emptying (Fig. 1). Pyloric obstruction was thus inferred. "Pseudotumors" were again observed.

Barium enema examination was performed one day later. An attempt to reflux barium past the ileocecal valve was successful, and the small bowel was flooded. Multiple films were obtained both before and after evacuation (Figs. 2 and 3). The small bowel mucosal pattern was diffusely abnormal with many distortions, such as thickened spikey folds, areas of folds with a stacked coin appearance, contour defects representing thumb printing, and increased separation between the barium filled loops. All of these changes were interpreted as due to bleeding into the wall of the small bowel. The duodenum was not visualized, but was presumably involved to explain pyloric obstruction. The colon was normal.

The child was treated conservatively and improved steadily except for one short episode of pain and vomiting some days later. He was completely well clinically in about two weeks.

Discussion

Anaphylactoid (Henoch-Schoenlein or allergic) purpura is manifested by purpuric bleeding into the skin, joints and gut. The small bowel pattern illustrated by the case presented is the classical appearance associated with bleeding into the bowel wall (1). Localized and diffuse intramural and sub-mucosal collections of blood give rise to thickened spikey folds, stacked coin appearance, and thumb printing, while the bowel wall thus thickened is responsible for increased distance between adjacent barium filled loops. The enlarged loops of bowel are also responsible for the appearance of pseudotumors seen on the plain film study. Pseudotumors are usually seen in cases of small bowel obstruction where the bowel loops are filled with fluid but no gas, so that no fluid levels are apparent with horizontal ray film; their appreciation is thus an important clue to the presence of the obstruction.

Pyloric obstruction prevented visualization of the duodenum, which presumably was also involved. This sequence of events is not uncommon, since the duodenum often presents the classical findings. Flooding the small bowel in retrograde fashion was employed to visualize the small bowel loops and to establish the diagnosis, and this technique, sometimes referred to as small bowel enema, should not be neglected as a method for clarifying the question of mechanical obstruction versus paralytic ileus, and delineating points of small bowel obstruction and other kinds of small bowel pathology.

Treatment in anaphylactoid purpura should always be conservative rather

than surgical if at all possible. The process is almost always self-limited, and the abdominal symptoms usually regress without sequelae.—H.M.P.

Case Report: SMALL BOWEL APPEARANCE IN ANAPHYLACTOID PURPURA.

Acknowledgment

This case is presented through the courtesy of Dr. Lawrence Shapiro, Good Samaritan Hospital, Suffern, New York.

References

1. Khilnani, M. T., and Hauser, A. D.: Intramural Intestinal Hemorrhage, *Med Times* 96:1058, 1968.

CASE NO. 336

SUBMITTED BY MELVIN R. SHEVACH, M.D.

A 42-year-old white male suddenly developed pain in the left flank and abdomen 20 hours prior to admission. There were no accompanying urinary symptoms or hematuria. The admission diagnosis was a renal stone, and the patient was treated with analgesics.

Physical examination revealed an acutely ill, pale, obese white male complaining of severe abdominal pain. The abdomen was exquisitely tender in the left upper quadrant and left flank, accompanied by guarding and spasm. Through the spasm one could feel an ill-defined left upper quadrant mass.

Chest x-ray revealed a left pleural effusion. Intravenous pyelogram revealed no definite excretion on the left side. There was a slight nephrogram effect at the upper pole only. A large 8 cm mass was seen at the lower pole, associated with two small nondiscript calcifications. The left psoas margin was obscured, while the soft tissues medial, and just below the lower pole exhibited a mottled quality and a series of lucent stripes with a linear striated effect (Fig. 1). An infusion pyelogram with laminograms was next performed. The features in and around the lower pole were again seen, but to better advantage (Fig. 2). In addition, laminograms revealed a thick wall to the mass with a lucent center. The findings were felt to be compatible either with a renal neoplasm or an abscess, in either case with infiltrations into the perirenal fat and soft tissues.

Renal angiography was next performed, and revealed numerous tumor vessels in relation to the left lower pole mass. The center of the mass was avascular, presumably necrotic, and the calcifications seemed related here. The striated soft tissues medial to the kidney did not opacify, and no unusual vessels were seen here (Fig. 3).

Left radical nephrectomy was performed. The pathologist described a large hypernephroma with central necrosis occupying the lower pole. There was extension of the tumor into the perirenal tissues. However, there was an additional large bulk of tissue medial to the kidney; this represented a massive



Case 336, Fig. 1. Anteroposterior abdominal radiograph from intravenous pyelogram made 30 minutes after injection reveals a slight nephrogram effect in the upper portion of the left kidney, but no delineation of the internal structures. A large 8 cm rounded mass is seen at the lower pole. The psoas margin is ill-defined. There is increased soft tissue density medial to, and just below the kidney, with mottled lucent shadows and a linear striated effect. Two small nondescript calcifications overlie the lower pole mass. The right tract and bladder are normal.

Case 336, Fig. 3. Early arterial film from selective left renal arteriogram reveals a grossly abnormal pattern of tumor vessels at the lower pole of the kidney in relation to the mass. A very large capsular branch crosses over the top of the kidney and extends down the lateral aspect to the region of the mass. Another stretched and straightened vessel courses along the medial aspect of the kidney. No opacification or abnormal vessels are seen in the medial pararenal soft tissues.

Case 336, Fig. 2. Coned view of the left kidney from infusion pyelogram reveals the findings described in Figure 1 to better advantage. Laminograms revealed the mass to be lucent in the center with an opacified thick peripheral rim. No opacification was seen in the medial pararenal soft tissues.



Case 336, Fig. 3



Case 336, Fig. 4. Photograph of the bisected specimen (frontal view, opened from left to right) graphically demonstrates the massive pararenal hematoma which extends superiorly to the adrenal. The tumor is seen at the lower pole with extension to the perirenal tissues.

hematoma which had dissected about the kidney into the perirenal fat and soft tissues in a striated fashion. The adrenal was measurably separated from the kidney by the hematoma. It was the pattern of the dissecting blood which resulted in the linear lucent stripes with the striated effect (Fig. 4).

Discussion

The radiographic findings are those of a typical necrotic hypernephroma of the lower pole of the left kidney. This case is of interest primarily because of the perirenal features. Hemorrhage around the kidney created a pattern of striated lucencies. These abnormal findings suggested neoplastic or inflammatory infiltration, until the gross pathology established the correct nature of the shadows.—H.M.P.

Case Report: HYPERNEPHROMA WITH MASSIVE PERIRENAL HEMATOMA.

Acknowledgment

This case is presented through the courtesy of Drs. Fred Graziano and Florian Yandel, Good Samaritan Hospital, Suffern, New York.

Received for publication June 3, 1969

Afterloading Multiple Irradiators for the Treatment of Cancer of the Corpus of the Uterus:

A Preliminary Report of a New Device

NORMAN SIMON, M.D.†

For decades, an effective radiation treatment for cancer of the fundus of the uterus has been the packing of the uterine cavity with multiple irradiators, Heyman applicators. Although effective, this method of treating cancer of the fundus of the uterus has two important disadvantages: unnecessary radiation exposure to personnel, and inaccuracy associated with the surgical handling of radioactive material. The afterloading devices described in this report eliminate completely radiation exposure to operating room personnel and reduce greatly the exposure to the radiotherapist. These devices also increase significantly the accuracy of placement of the radioactive material.

In the radiation treatment of cancer of the fundus of the uterus by the Heyman technique, the uterine cavity is packed with metallic capsules, each containing 8 to 10 mg of radium. As many capsules are inserted into the uterus as its cavity can hold, usually 3 to 12. A stainless steel wire about 25 cm long is attached to each capsule, and these wires lead out of the cervix and vagina to permit removal of the radium upon completion of the treatment in 48 to 72 hours. Heyman capsules are available in the radium supply of a hospital or they may be rented from a radium dealer. Ordinarily, the diagnosis of adenocarcinoma of the uterus is established by diagnostic curettage and biopsy under general anesthesia. When the pathologist's report of the biopsy specimen is positive for cancer, the patient is anesthetized once again, and the Heyman capsules are inserted, one at a time, into the uterine cavity through the dilated cervix. During this packing procedure, the prudent radiotherapist proceeds rapidly in order to reduce the radiation exposure to himself and the operating room personnel to a minimum, but he may receive as much as 50 to 100 mR, as measured by ionization chambers in his breast pocket. As the operator tends to work rapidly, the accuracy of placement of the radium capsules may be compromised.

Afterloading techniques have been developed to reduce radiation exposure to personnel in the implantation of radioactive materials, and to increase the accuracy of placement of radioactive sources. In these techniques, empty tubes or needles are implanted directly into tumors, and subsequently the radioactive sources are inserted. The method has been applicable in the direct implantation of tumors with radioactive material, and, in the treatment of cancer of the uterine cervix, afterloading techniques are almost becoming standard. In the treatment of cancer of the uterine cervix, the radium system is comprised essentially of a tandem to be inserted into the uterine cavity and ovoids in the

† Associate Clinical Professor of Radiotherapy, the Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

vault of the vagina. This relatively simple array permits afterloading of the hollow tandem and ovoids, and several satisfactory systems for this purpose are now in general use.

When *multiple* capsules of radioactive material are required for packing the uterine cavity in the case of adenocarcinoma of the uterus, afterloading is not so simply performed. Radium sources are dimensionally too large to afterload into numerous capsules; high specific activity radioactive materials must be substituted for radium in order to develop an afterloading system.

Description of New Afterloading Irradiators for Packing the Uterus

Nylon capsules 2 cm in length and 6 mm in diameter have narrow cavities within them with long plastic thin hollow tubes 40 cm long communicating with the cavity. The diameter of the cavity in the capsule and the internal diameter of the tube can accommodate the miniaturized radioactive sources, in this instance, Cesium-137. The outer diameter of the tube must not exceed 2 mm, because the tubes from all the intrauterine capsules come together at the cervix to pass through the vagina to the introitus. After the empty capsules are packed into the uterine cavity, the radioactive material is inserted into each of the capsules via its tube.

Technique of Application

When a patient with postmenopausal bleeding, suspect of having cancer of the fundus of the uterus is having a diagnostic curettage, and while she is still under anesthesia, the empty afterloading capsules are packed into the uterine cavity. The patient is returned to her room after operation to await the results of the biopsy. If the tissue proves to be adenocarcinoma, the empty capsules are loaded by inserting the Cesium-137 into each capsule through its connecting tube lying outside the introitus. This procedure is performed in the radiotherapy department or the patient's room. It does not require the operating room or anesthesia. If the biopsy specimen proves to be benign, the empty capsules are simply removed.

The Advantages of this Afterloading Method of Treating Cancer of the Fundus of the Uterus

1. *Safety.* Unnecessary exposure to radiation of personnel in the operating room, recovery room, and x-ray department is avoided. Only after the blank capsules are in the desired position is the radioactive material inserted, and this can be done rapidly with little exposure to anyone but the patient.

2. *Accuracy.* The radiotherapist or surgeon who packs a uterine cavity directly with radium often accepts a compromise with the ideal distribution, for the procedure is likely to be performed in haste when radium is being handled. Afterloading capsules may be positioned accurately, without haste.

3. *Convenience.* Empty sterile afterloading capsules of various sizes may be kept available in the operating room, and advance preparation for radioactive materials need not be made in the event a patient is having a dilatation and


curettage for postmenopausal bleeding. If the uterine cavity is packed with these blank capsules directly after biopsy, even before the specimen has been examined pathologically, the patient is spared an extra operative procedure and anesthesia.

The first patient with adenocarcinoma of the uterus who was treated with the method had a small uterus accommodating only 3 capsules within its cavity. Two capsules were also placed in the vaginal vault, one in each lateral fornix. After roentgenograms confirmed proper positioning, each of the 5 capsules was quickly loaded with a Cesium-137 source contained in the tip of an 18 gauge stainless steel tube. The insertion of radioactive material was effected with a dose of less than 2 mR to the radiotherapist's breast pocket ionization chamber.

Summary

A newly described afterloading method for packing the uterine cavity with multiple irradiators in the presence of adenocarcinoma of the fundus appears to be practical and promising. Each irradiator is a plastic capsule with a hollow thin tube connecting its cavity to the outside. After the capsules have been packed into the uterine cavity, small sized sources of high activity radioactive material are loaded into the devices. Accuracy is increased, radiation exposure to operating room personnel is nil, and exposure to the radiotherapist and other hospital personnel is sharply reduced.

Received for publication June 20, 1969



**Forecast:
arthritic
flare-ups**

In Memoriam

ROBERT K. LIPPMANN, M.D.

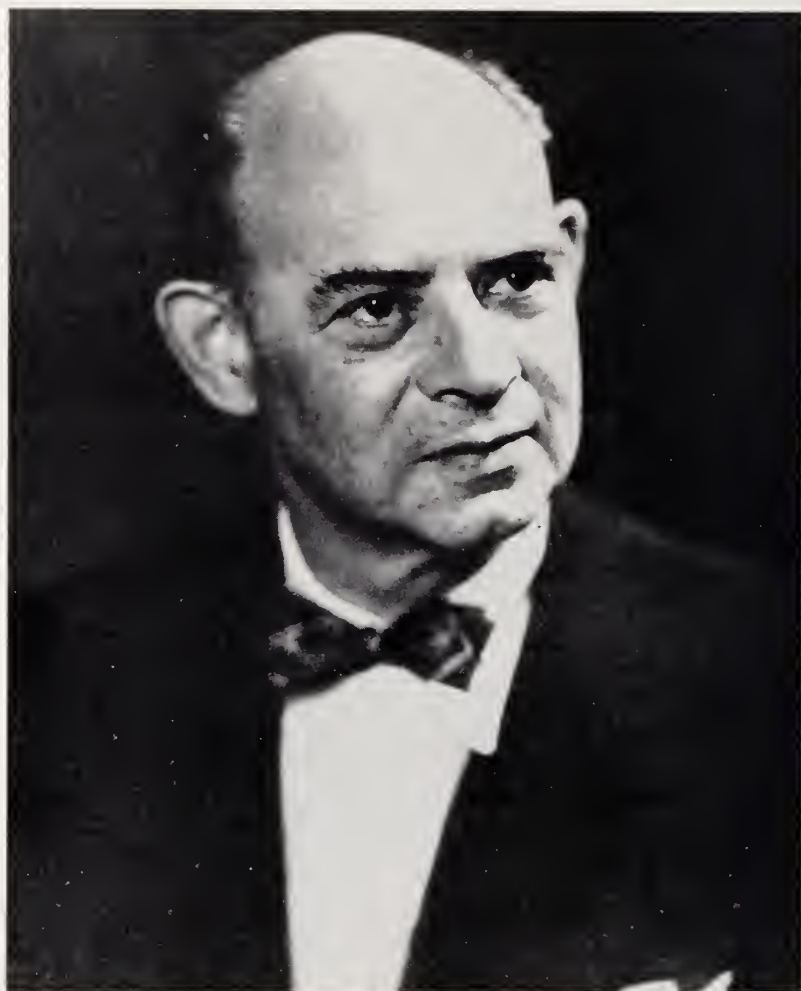
1898-1969

Until his untimely and sudden death on June 9, 1969 at the age of 70, Dr. Robert Korn Lippmann was actively engaged in orthopaedic practice. He was looking forward, as he did each year, to spending the summer at his home in Stamford, and commuting to his office and hospital.

Dr. Lippmann was born and educated in New York. He graduated from De Witt Clinton High School in 1915, and Columbia University in 1918, where he received a B. S. degree. From 1918 to 1922 Dr. Lippmann was a medical student at Johns Hopkins, and was one of several graduates who became internationally prominent in orthopaedics. From 1923 to 1925 he was an intern at The Mount Sinai Hospital. His first year in orthopaedics was spent studying bone pathology in Vienna in the laboratory of Professor Erdheim, where he was introduced to a basic scientific approach to the specialty which remained the foundation of much of his future work. In 1925 he also studied under Professor Putti at the Istituto Rizzoli in Bologna. On his return to The Mount Sinai Hospital in 1926 as Adjunct Orthopaedist, Dr. Lippmann joined his Chief of Service, Dr. P. William Nathan, in practice. He began investigating the pathology and etiology of osteochondritis of the hip in children. His descriptions of avascular necrosis, and experimental, pathological, and clinical findings in Perthes Disease are well known.

While Adjunct, and then Associate Orthopaedic Surgeon and Chief of the Orthopaedic Clinic at The Mount Sinai Hospital, Dr. Lippmann also served as Adjunct Orthopaedic Surgeon and Associate Orthopaedic Surgeon at Montefiore Hospital. At Montefiore, he became Chief of the Service in 1938, but resigned in 1942, 3 years after he became Director of the Department of Orthopaedic Surgery and Orthopaedic Surgeon-in-Chief at The Mount Sinai Hospital. Under Dr. Lippmann's leadership, the service grew rapidly to become a fully board-approved residency training program in fractures, and adult and children's orthopaedics, into which basic sciences were integrated. By liaison with Blythedale, a longterm children's care hospital in Valhalla, New York, where Dr. Lippmann served as Orthopaedic Surgeon-in-Chief for almost 30 years, the training program was greatly expanded. He also served on the Executive Committee of the Medical Board of The Mount Sinai Hospital for many years, was President of the Medical Board in 1960, Consulting Orthopaedic Surgeon, Director Emeritus of Orthopaedics, and Emeritus Professor of the Department of Orthopaedics of Mount Sinai School of Medicine.

Dr. Lippman introduced both a clinical and laboratory investigative ap-



ROBERT K. LIPPMANN, M.D.

1898-1969

proach, and stimulated staff and residents to participate in studies including bone healing, growth, induction, and transplantation. Dr. Lippmann was a superb craftsman, capable of translating his mechanical concepts into reality.

In his office was a workshop with power tools and a lathe to work out the designs of devices that were later fabricated, or new instruments to facilitate his surgery. Among his many original contributions were a compression bolt for fractures of the hip, spike osteotomy of the femur in children, repair of tibial condyle fractures, a transfixing hip prosthesis, etiology and treatment of adhesive capsulitis and parainflammatory joint instability, and auscultatory percussion of bone as a means of detecting fractures and assessing their progress of healing. The Robert K. Lippmann Orthopaedic Research Laboratory was established in 1965 on this tradition of research in orthopaedics.

In addition to his hospital practice, Dr. Lippmann participated in community, national, and international orthopaedics. He was a Fellow of the American Academy of Orthopaedic Surgeons (1932) and the American College of Surgeons (1932), and a member of its New York and Brooklyn Regional Fracture Committee (1949). He was also a Fellow of the New York Academy of Medicine: Secretary (1949-50); Chairman of the Orthopaedic Section (1950-51); and a member of the Advisory Committee (1951-56). He was a member of the American Orthopaedic Association (1954), the International Society of Orthopaedic Surgery and Traumatology (SICOT) in 1957, and of the Orthopaedic Research Society (1959). Dr. Lippmann was Secretary (1950) and Chairman (1951) of the Orthopaedic Section of the New York State Medical Society, and a member of the Advisory Committee to the Commissioner of Health (1957-60).

Dr. Lippmann developed a spirit of cooperation and dedication on the orthopaedic service. He encouraged free discussion, disagreements, and thorough exploration of clinical problems as his basic technique in residency training. Dr. and Mrs. Lippmann expressed their friendship in their many contacts with the residents and staff, particularly at the monthly evening Journal Club meetings at their home in New York and at their summer home in Stamford. In the back of his mind was always the idea that he would some day describe the principles of conservative orthopaedics that he taught—a task that must be completed by his students.

Dr. Lippmann was a sensitive man with a deep feeling for family and friendship. His interests were broad, and he refused to remain only a spectator. While at Columbia, he collaborated with Oscar Hammerstein and composed the music for several Columbia Varsity Shows. It was suggested that he become a musician instead of a physician. He became both. He made medicine his vocation, and piano and organ music his avocation.

Stamford fulfilled his need to be out of doors in the country working with his hands, and close to his wife Helen, his family, and friends. At the time of his death, he was returning to his office after 10 days in Stamford, happy and busy doing the things he loved so much. Dr. Lippmann is survived by his wife;

his daughter, Mrs. Nancy L. Heon; his son, Robert D. Lippmann; and his 4-year-old grandson, R. R. Dennis Heon.

At The Mount Sinai Hospital, Dr. Lippmann's service and leadership over a period of 43 years, his scientific inquiry and teaching, and sense of humanity and ethical code of practice in his approach to patients, formed the foundations of the orthopaedic service and had great influence on the growth of the hospital as a whole. By those who were fortunate enough to know him, Dr. Lippmann will be remembered with respect and great personal warmth. Those of us who were his students will miss him sorely.

ROBERT S. SIFFERT, M.D.
for the
EDITORIAL BOARD

In Memoriam

ARTHUR SCHIFRIN, M.D.

1904-1969

Arthur Schifrin was born in New York City on March 22, 1904, graduated from Columbia University with an A.B. degree in 1924, and from the Columbia University College of Physicians and Surgeons with an M.D. degree in 1927, where he was also elected to Alpha Omega Alpha. He was an intern in pathology at The Mount Sinai Hospital for 1 year, and then spent 2½ years in an appointment in medicine, culminating as House Physician in 1930. From 1931 to 1932 he studied in Berlin at the Pathologic Institute, Charité Hospital, and at the Rudolph Virchow Krankenhaus.

He returned to America and to The Mount Sinai Hospital in 1932, holding an Arthur Lorsch Fellowship in Pathology. From 1932 to 1936 he was Research Associate in the Department of Morbid Anatomy at The Mount Sinai Hospital. Additionally, he became Research Associate at the Beth Israel Medical Center in New York, and served many years at the Gouverneur Hospital, rising to be Director of its Department of Medicine. He was with the Port of New York Authority from 1942 until his death, first as Deputy, and then as Chief Medical Director. Although his clinical interests rose, and even though he advanced in the hierarchy in the Department of Medicine of The Mount Sinai Hospital, first as Adjunct Physician, and then as Associate Attending Physician, he never lost a passion for morbid anatomy and clinical investigations with the then newer biochemical methods. At his death, he was Assistant Professor of Medicine at the Medical School.

In 1938, with Dr. George Baehr and Dr. Paul Klemperer, he wrote the original description of the "wire loop" lesion of lupus erythematosus. With his associates, he described the decrease in serum cholinesterase in jaundice and biliary disease, one of the early descriptions of serum enzyme changes in disease. He described the striking rise of serum amylase after the administration of cholinesters. Other papers of importance also came from his meticulous work.

In addition to his laboratory investigations, which were for him a labor of love, and his demanding clinical hospital duties, Dr. Schifrin maintained a private practice to which he gave of himself without stint, and without thought of material reward. His patients worshipped him, and well they might have, for his involvement in their problems was total and complete. His devotion to his wife, Frances, and his daughters, Carol and Audrey was unique, but was what one would have expected of him.

Benign but not sentimental, gentle but strong, with the strength that only the truly gentle have, patient, giving, tolerant, and forbearing, Arthur Schifrin radiated goodness. He loved all fellow humans, and in return they loved him. He was humble—not the humility of self-abnegation, or of timidity, or



ARTHUR SCHIFRIN, M.D.

1904-1969

the cloak for an underlying vanity, but the humility that stemmed from the profound conviction that all souls have equal worth. This was not an article of faith to be trumpeted, but so much a part of his warp and woof that it never came to consciousness, was never articulated or voiced, but only lived out in all his contacts: personal, social, and professional. He helped everyone, he failed no one. Only as a scientist was he demanding, and there his incisive, fertile, inquiring mind was vigorous and severe. For all who knew him, and regardless of how remote or tangential the contact, his life was a blessing.

WILLIAM ANTOPOL, M.D.

LESTER R. TUCHMAN, M.D.

for the

EDITORIAL BOARD

The Health of the Fetus during Labor*

STANLEY G. CLAYTON†

The name of Dr. I. C. Rubin will always be remembered because of his great contributions to the study of infertility and of tubal function. I hope that he would have approved of our subject for today, for fertility demands more than conception—the fetus must be carried and then safely delivered.

According to the dictionary, a middleman is “a trader through whose hands a commodity passes from producer to consumer,” and the word is often used in a derogatory sense, implying that the middleman is having an easy living at the expense of those who do the real work. You see a middleman before you; as Chairman of a Department and as Editor of a Journal, I realize that I have now become a middleman who markets the thoughts of others. In thanking you for the honour of this invitation, I accept it for my group, not for myself, and my chief task will be to review our experience of fetal blood sampling in practical obstetrics.

Consideration of the health of the fetus during labour is of importance to us all. After we have passed the first 4 months of intrauterine life, we have a greater risk of death during birth than for many subsequent years. After its comfortable and idle sojourn in the uterus during pregnancy, the fetus is suddenly subjected to several hours of intermittent, but severe, compression, involving both its head and its placenta.

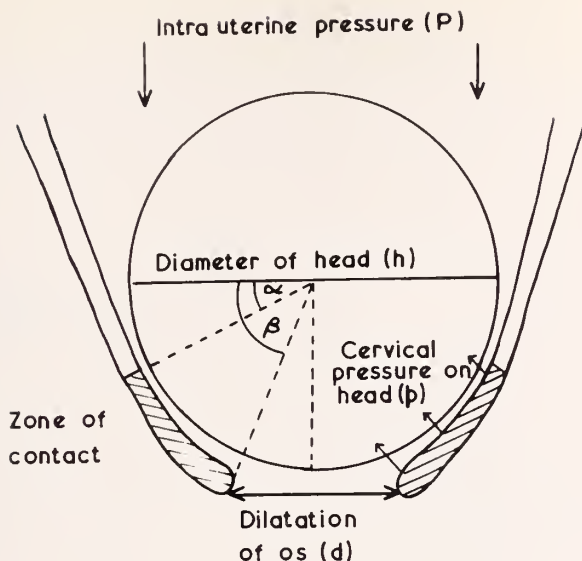
Compression of the fetal head causes bradycardia (1, 2), especially when the cervix is between 4 and 8 cm dilated. Although this has been denied by Smyth (3), most of us accept the evidence of Hon and his associates on this point. To produce the moulding of the head which is commonly observed, it seems obvious that considerable pressure is needed. Figure 1 shows the results of a theoretical calculation. If the downward component of the intrauterine pressure (P) is equal to the upward component of the pressure of the lower segment and cervix on the head (p), then it can be shown that

$$\frac{P}{p} = 1 - \frac{d^2}{h^2} - \sin^2 \alpha,$$

where h is the diameter of the head, d is the dilatation of the cervix, and the angle α depends on the application of the head to the lower segment. Although the calculations are somewhat artificial, as the system is not static, and the shapes of the structures vary from case to case and from time to time during labour, Table I shows that the pressure of the cervix on the head will exceed the intrauterine pressure in late labour. The intracranial pressure must be in-

* Presented as the I. C. Rubin Commemoration Lecture, March 13, 1969, The Mount Sinai Hospital, New York, N.Y. 10029.

† Professor of Obstetrics and Gynaecology, King's College Hospital Medical School, University of London, London, England.



$$\frac{P}{p} = \sin^2 \beta - \sin^2 \alpha$$

$$= 1 - \frac{d^2}{h^2} - \sin^2 \alpha$$

FIG. 1. Theoretical relationship between intrauterine pressure (P) and cervical pressure on head (p).

intermediate between these pressures; such pressure differences are possible because of the partial rigidity of the skull.

As long as intracranial haemorrhage does not occur, bradycardia resulting from intermittent compression of the head may not harm the fetus, and the only difficulty is in the diagnosis of the cause of the bradycardia. Even if it is not accepted by everyone that compression of the fetal head causes slowing of the fetal heart, there can be no doubt that the heart rate often slows during uterine contractions. Hon (4), and Caldeyro-Barcia et al (5) have described various patterns of change which can be recognized by the use of accurate ratemeters.

From time to time, transient rises in rate occur without reference to uterine contractions, especially after the fetus has received some stimulus, as from manipulation or a needle. The fetus will respond to a loud noise or even to transillumination of the abdomen by a bright light (6). Such responses are assumed to be due to sympathetic activity. In addition, tachycardia occurs with hypoxia, and the clinical importance of this sign has not been sufficiently appreciated. Further reference will be made to this later.

We may for a moment recapitulate what is well known. With uterine contractions, two types of response are seen (Fig. 2). These have been called

TABLE I
Examples of Cervical Pressure

Diameter of Head (cm)	Diameter of Os (cm)	Ratio of Cervical Pressure to I U Pressure
$\alpha = 0^\circ$		
9.5	1	1.0
	5	1.4
	7	2.2
	8	3.4
	9	9.7
12.0	1	1.0
	5	1.2
	7	1.5
	9	2.3
	10	3.3
	11	6.2
$\alpha = 30^\circ$		
9.5	1	1.3
	5	2.1
	7	3.1
	7.5	7.9
	8	24.0
12.0	1	1.3
	5	1.7
	7	2.4
	8	3.3
	9	5.3
	9.5	8.0
	10	18.0

Type I and Type II dips in the heart rate. Type I dips are V-shaped, and occur soon after a contraction. They occur most frequently in late labour, after the membranes have ruptured. This pattern of dip is abolished by atropine, and this response is seen in association with compression of the fetal skull.

Type II dips are U-shaped, and occur at a longer interval after the contraction. They are deeper and more prolonged than V dips. They are associated with fetal hypoxia, and occur at any stage of labour. Atropine has only a slight effect upon them. Slowing of the fetal heart during hypoxia may be advantageous at first, as the myocardium is protected, and it is fascinating to find that a similar bradycardia occurs in seals during deep dives. If, however, the U dips occur frequently and coalesce, then the heart rate becomes persistently slow, and this will interfere with placental exchange and with the transport of oxygen to the fetal tissues. Figure 3 shows the possible physiological mechanisms involved.

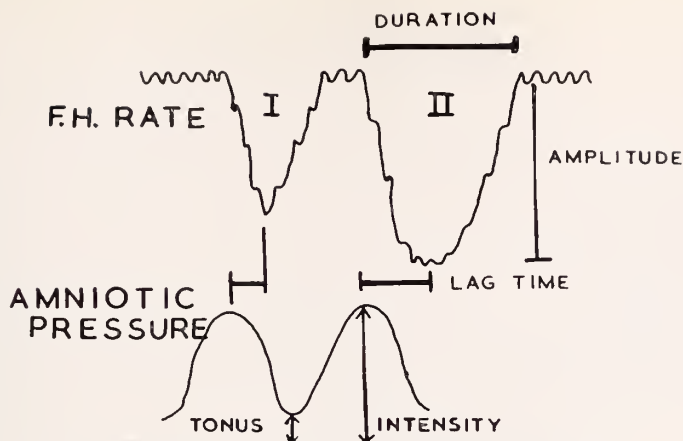
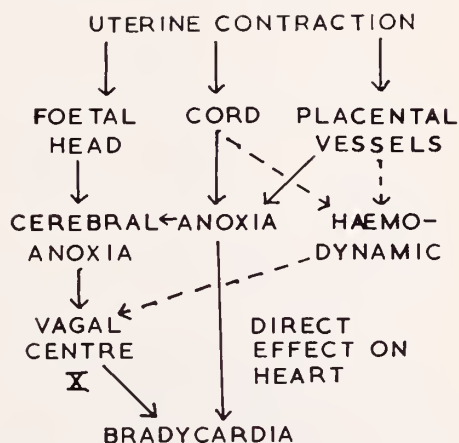


FIG. 2. Type I and Type II dips in fetal heart rate.

FIG. 3. Possible physiological mechanisms for fetal bradycardia.



Except in research centres, accurate ratemeters are unlikely to be available. Most clinicians still have to rely on simple auscultation, but Caldeyro-Barcia et al (5), and Day, Maddern, and Wood (7) have pointed out that if proper methods of counting are used, then Type II dips can be recognized. The observer should count for discrete 10 second intervals over a period of 2 minutes in relation to a uterine contraction.

Far too little attention has been paid to tachycardia as a sign of fetal distress. Coltart, Trickey, and Beard (8) recently studied 195 cases with clinical evidence of fetal distress, and found that tachycardia alone was the warning sign in 128 instances. In addition, fetal blood samples showed that in 20 percent of the cases of tachycardia there was a significant change in the pH of the blood. They had 57 cases with bradycardia alone, and only 7 percent of these were found to have acidaemia (Table II). It is, of course, probable that the tachycardia would have progressed to bradycardia in many of the cases, but a rapid fetal heart rate must be studied at once.

TABLE II
Cases with Clinical Evidence of Fetal Distress
(Collart, Trickey, and Beard, 1969)

	Clinical Fetal Distress	Acidaemia*
Fetal heart rate >160.....	128	26 (20%)
Fetal heart rate <120.....	57	4 (7%)
Meconium with normal F H R.....	67	6 (11%)
Meconium with abnormal F H R.....	43	9 (21%)
Total.....	295	45

* pH less than 7.25 in first stage, or less than 7.20 in second stage.

TABLE III
Cases with Clinical Evidence of Fetal Distress
(Day, Maddern, and Wood, 1968)

No. of Cases	F H R	Liquor	Mean Apgar Score
11	>160	Clear	5.5
27	>160	Meconium	5.0
10	<120	Clear	7.9
14	<120	Meconium	6.8
53	Normal	Meconium	7.1
29 (Controls)	Normal	Clear	7.0

Table III summarizes observations made by Day et al (7), which also show that tachycardia may be the only sign of serious fetal distress. This is especially the case if persisting tachycardia is associated with Type II dips, or with slowing that persists after each contraction.

The mechanism of these changes in the fetal heart rate with hypoxia has been much discussed. It is likely that tachycardia is due to increased sympathetic activity. A similar effect is produced by injecting adrenaline into the fetus; in the lamb, the chemoreceptors, especially the aortic receptors, are active (9).

The fetus has its own homeostatic mechanisms, and it actively regulates its own internal environment. It might be supposed that the fetal blood gas concentrations would be directly dependent on those of the mother, but the relationship is far more complicated. If the maternal oxygen tension falls, the fetal oxygen tension changes much less for the following reasons:

(1) The fetal oxyhaemoglobin dissociation curve is "to the left" of the maternal curve. At oxygen saturations below 60 percent, a relatively large fall in oxygen content occurs without much fall in oxygen tension. If the pH of the maternal blood falls at the same time because of accumulation of acid metab-

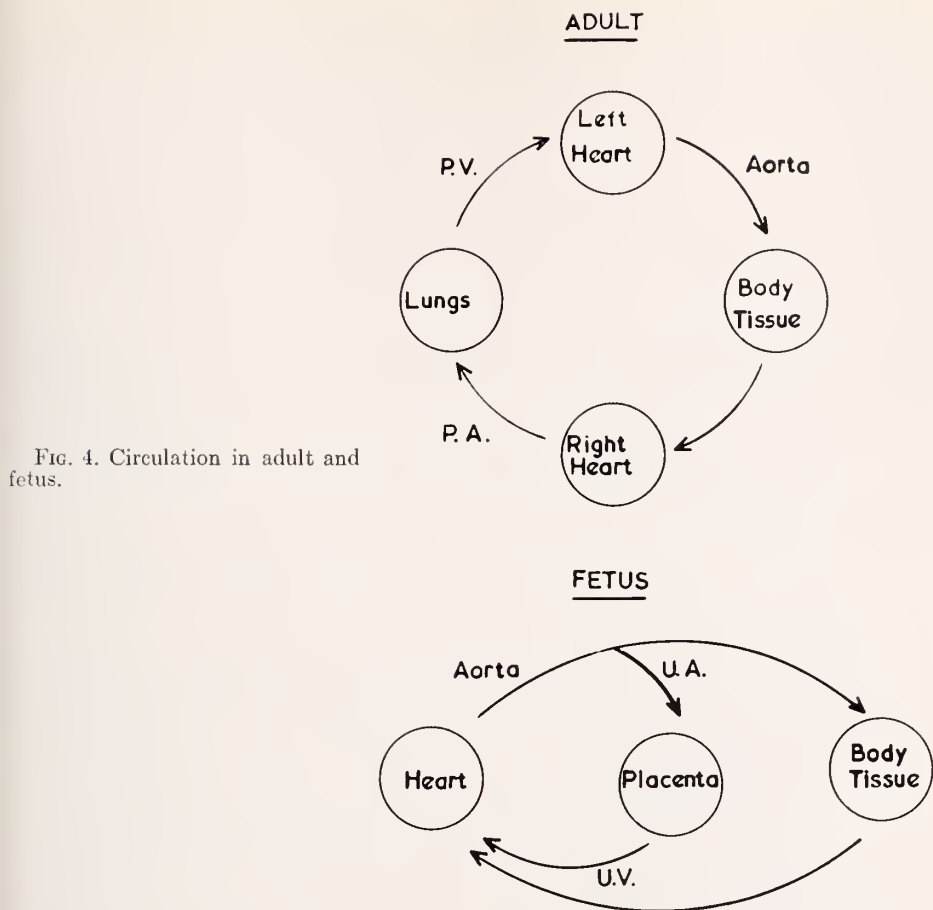


FIG. 4. Circulation in adult and fetus.

olites during labour, the maternal dissociation curve is shifted further to the right of the fetal curve by the Bohr effect, so that the fetal blood is at an even greater advantage. Of course, the pH of the fetal blood will eventually fall too, so this advantage is only temporary.

(2) Dawes (9) has pointed out that in the adult the circulation through the lungs and body tissues is in series, so that even if the tissues consume more oxygen, the arterial oxygen tension will not change so long as the blood in the pulmonary veins is well oxygenated. In the fetus, the circulation through the placenta and that through the body tissues are in parallel (Fig. 4), so that if the tissues take up more oxygen, the arterial oxygen tension will fall. But, conversely, if the oxygen consumption of the fetal tissues is reduced, and other factors are unchanged, the arterial oxygen tension will rise. It is therefore possible for the fetus to regulate the arterial oxygen tension to some degree by altering the total consumption of oxygen by the tissues. If, during hypoxia, the fetus can reduce the oxygen consumption by its less vital organs, the oxygen tension of the blood supplying the brain and heart will be maintained.

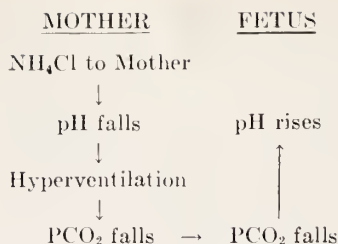


FIG. 5. Effect of administration of ammonium chloride to the mother.

Acheson, Davies, and Mott (10), and Dawes, Mott, and Shelley (11, 12) have shown that the total oxygen consumption of the fetal lamb falls when the arterial saturation is less than 50 percent. During hypoxia the distribution of the fetal blood flow is altered. If the umbilical blood flow is reduced in fetal lambs there is a relatively greater fall in femoral than in carotid oxygen saturation (12), indicating that the vital coronary and cerebral oxygen supply is being conserved.

(3) The placental tissues themselves have a high oxygen consumption (13). I do not know if anyone has yet investigated the effect of hypoxia on the oxygen consumption of the placenta.

During either maternal or fetal acidemia, compensatory mechanisms operate. The placenta seems to be freely permeable to carbon dioxide, and maternal and fetal PCO_2 levels are directly related. The rate of transfer of lactate across the placenta is less certain. Friedman et al (14) showed that lactic acid passes freely across the placenta in monkeys, and Daniel, Adamsons, and James (15) showed that the normal human placenta is permeable to lactate, but that transfer is less effective when placental function is impaired, as would be the case with hypoxia.

It is possible that the placenta is less permeable to bicarbonate (16). In several species, Meschia, Battaglia, and Barron (17), and Dancis, Worth, and Schneidau (18) showed that administration of ammonium chloride to the mother caused a fall in arterial pH, with hyperventilation and a consequent fall in PCO_2 . The chloride did not appear to pass across to the fetus. Although the fetal PCO_2 also fell, there was a *rise* in fetal pH, as the fetal plasma bicarbonate did not alter quickly (Fig. 5). These experiments have been criticized for a variety of reasons, but they suggest that the maternal and fetal pH values are not coupled as directly as the PCO_2 values.

During pregnancy, maternal hyperventilation occurs with a fall of PCO_2 to about 32 mm Hg (19). Because of compensatory excretion of bicarbonate by the kidneys, the base deficit is increased by about 2.5 mEq/L, and the pH of the blood is unaltered. This respiratory alkalosis and compensatory metabolic acidosis makes elimination of carbon dioxide by the fetus easier.

During labour, acids are released by maternal muscular activity and may be formed by maternal ketosis, but the pH of the blood shows little change as the base deficit increases still further.

An important practical question is whether administration of high concentrations of oxygen to the mother will increase fetal uptake and arterial tension. Discussion has arisen because animal experiments and placental perfusion experiments have shown constriction of fetal vessels with high oxygen tensions (20-22). The simple point seems to have been overlooked that in cases of fetal distress the fetal vessels are unlikely to be receiving high concentrations of oxygen, and the administration of oxygen for a short time may only bring the placental oxygen tension back to normal. Rivard et al (23) showed that although administration of oxygen to the mother of a fetus which was already well oxygenated produced little change in oxygen tension, if the fetus was asphyxiated, a large rise occurred. Caldeyro-Barcia et al (5) showed beneficial results in human pregnancy, as judged by the effect on Type II dips in the heart rate.

Observations on maternal hyperventilation during labour do not bear on this question. Motoyama et al (24), and Moya et al (25) showed that when the maternal PCO_2 reached 15 mm and the pH rose to 7.6, inhalation of oxygen caused a fall in fetal blood oxygen saturation. In cases of hypoxia, however, these conditions are not found.

After all these theoretical considerations, we may now turn to consider fetal distress during labour. The fetus may suffer from lesions of the placenta or cord, from injuries, or from the effect of drugs, but these I shall not discuss. Uterine contractions will affect the blood flow through the intervillous space. The venous outflow will be interrupted if the uterine pressure reaches 30 mm Hg, but fetal hypoxia will only occur if the contractions are unduly frequent or prolonged, without adequate relaxation between the contractions.

In 1963, at Queen Charlotte's Hospital, we heard of the work of Dr. Saling in Berlin on fetal blood sampling (26). For the next 4 years we used his method with increasing frequency, and it is the results obtained, particularly by Richard Beard, that I now present. We started hesitantly, but soon found that the research technique became part of the routine assessment in cases of fetal distress, and that even the most conservative colleagues began to take advantage of it. Of the technique, I need now say little. We found that it had dangers until the instruments were modified (27). We believe that the fetal risk has been completely overcome by the better design of the blade, and by the rule that a Singer test for fetal blood is to be applied whenever blood continues to escape from the vagina after the operation.

Apart altogether from blood sampling, Saling uses amnioscopy freely during pregnancy to examine the liquor through the intact membranes in cases of possible placental insufficiency. Kubli (28), Teramo (29), and Browne (30) have all reported enthusiastically about this. We noted that Saling said that the risk of rupturing the membranes at each examination was 2 percent, and that even if meconium was seen, only 18 percent of the fetuses ultimately showed evidence of hypoxia. We also knew that in some cases severe fetal distress occurred with clear liquor. For these reasons, we did not use this part of Saling's technique.

Dunstan has studied all the recent stillbirths in Queen Charlotte's Hospital to see which cases had indications for amniocentesis by Saling's criteria. Among 54 stillbirths occurring after 35 weeks gestation and before the onset of labour, indications for amniocentesis were present in only 8 cases (31). Huntingford performed amniocentesis on 290 women, or 10 percent of his patients. Only 16 patients had meconium in the liquor, and all of these went into labour without evidence of fetal asphyxia. In the same group of patients, 17 fetuses with clear liquor developed clinical signs of fetal distress during labour (31). It is possible that the good results reported after the use of amniocentesis depend less on the method than on close supervision of the patients.

At Queen Charlotte's Hospital, therefore, we did not use amniocentesis, but we used fetal blood sampling for patients in labour in whom there was: (1) clinical evidence of fetal distress; or (2) reason to suspect that there might be placental insufficiency. There is no need today to recapitulate how determination of the pH and base deficit of blood is used to assess respiratory and metabolic acidosis. James and his colleagues (32) showed that in clinical practice measurement of fetal acidemia was a better index of the duration and severity of hypoxia than estimation of the oxygen levels, which fluctuate so quickly. Questions are still asked about the reliability of the method (33, 34). Kubli (35), and McDonald (36) have shown that most samples give results that lie between those obtained from umbilical venous blood and arterial blood, if the samples are collected shortly before delivery. For good results a few practical points may be mentioned: (1) It is essential to clean and service the Astrup machine frequently, and one person should be responsible for checking it, and the buffer solutions, daily. The machine should be kept switched on, so that it is always ready at working temperature; (2) glass tubing is preferable to the original polythene tubing; (3) samples should be taken, when possible, during a contraction; and (4) while undue pressure on the scalp must be avoided, because this will impede the circulation and give falsely high readings of the PCO_2 , sufficient pressure to exclude liquor is essential. We found that most of the residents soon became skillful at collecting the samples and using the Astrup machine.

Our first task was to establish our normal levels, and Figures 6 and 7 show the results obtained by Beard and Morris (37) for pH and base deficit in normal cases. The pH did not fall below 7.25 in any normal case during the first stage of labour, nor below 7.20 in the second stage. These results agreed well with those of Saling (38). There is a slight increase in PCO_2 to about 47 mm Hg in normal labour, but also a slight increase in base deficit. At first, we took any pH of less than 7.20 as abnormal, but with increasing experience the rule was added that if any sample gave a result of less than 7.25, another sample was to be collected within a short time.

At the time of taking a fetal sample, we also examined the maternal blood, and found that some cases of fetal acidemia are secondary to maternal acidosis. Equilibration to determine the base difference will distinguish these cases, but they are few in number, and in a busy unit simple measurement

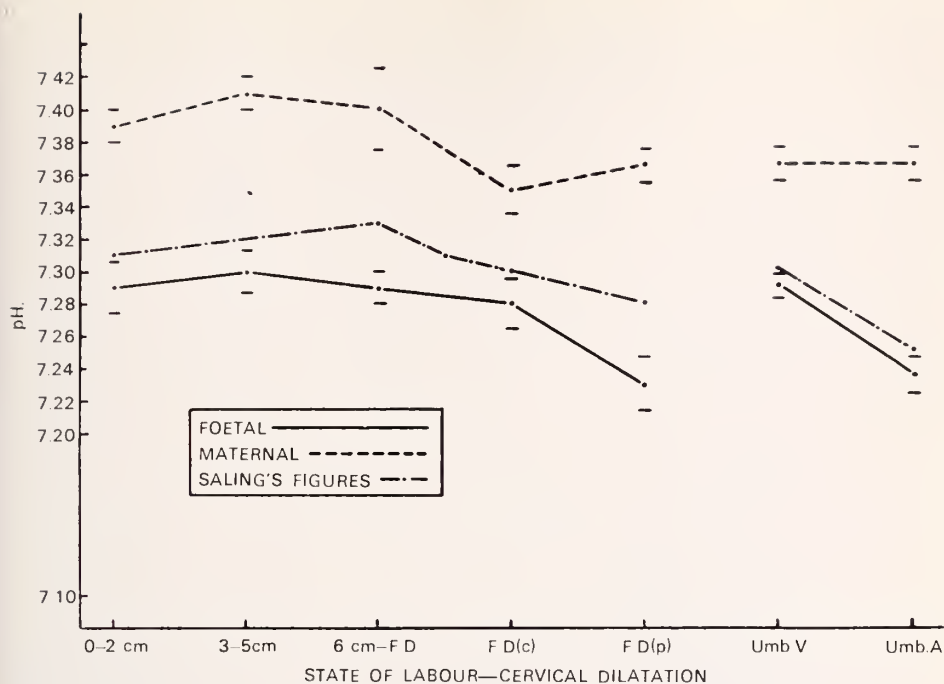


Fig. 6. pH changes in labour. Transverse bars represent standard errors.

F D (c) = full dilatation (head in cavity)

F D (p) = full dilatation (head on perineum)

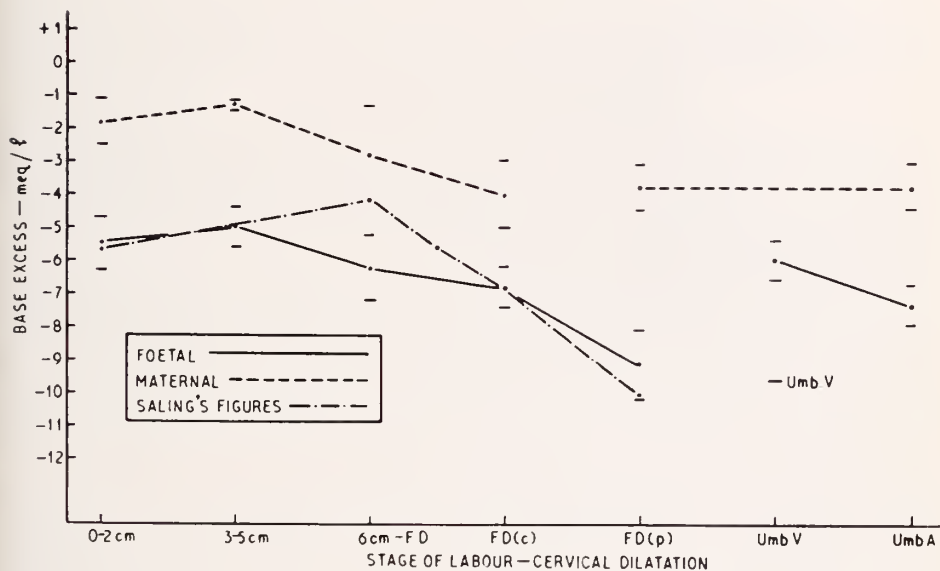


Fig. 7. Base deficit changes in labour. Transverse bars represent standard deviations.

F D (c) = full dilatation (head in cavity)

F D (p) = full dilatation (head on perineum)

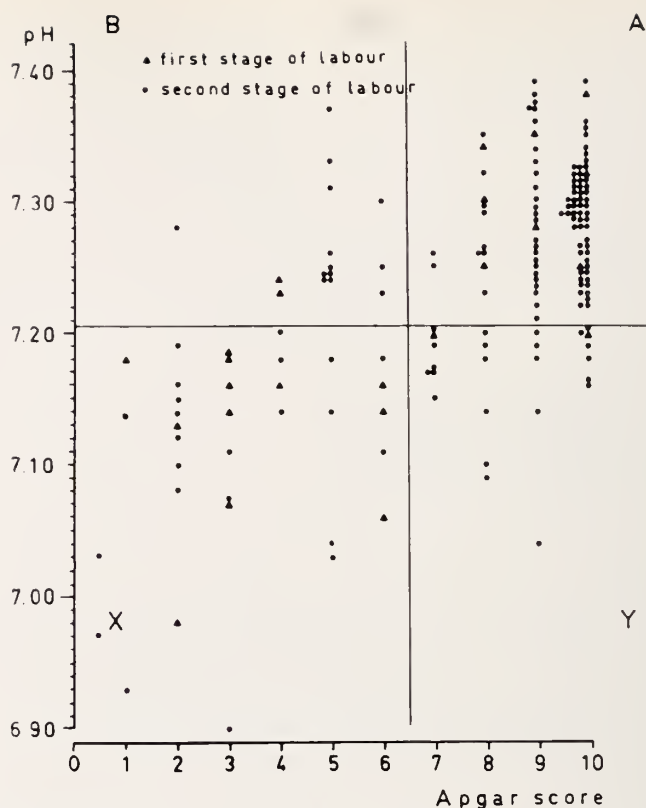


FIG. 8. Distribution of pH values of 176 samples of fetal blood relative to Apgar score 2 minutes after delivery.

▲ samples collected during first stage
● samples collected during second stage

of the fetal pH may be all that is possible, and this is still very useful. As a side issue, this investigation led us to take more care to correct maternal acidosis during labour, which is so often the result of the anxiety of the anaesthetists to withhold any form of oral feeding.

Another approach to the establishment of normal values is shown in Figures 8 and 9, which demonstrate that there is a broad relationship between the pH of the fetal blood, and the Apgar score after delivery (39). However, the biochemical results must never be divorced from the clinical observations; this technique does not supplant, but only complements, clinical observations, giving insight into the significance of the signs.

The difficulty with the signs of fetal distress is that they are unreliable. Fortunately, there are few cases in which a fetus perishes without clinical warning. In most cases it is the other way around—there are signs that call for operative delivery, but when the fetus is born, it is found to be in excellent condition. Yet, there are a few cases in which fetal blood samples, collected because the fetus is in a high risk group, show a progressive fall in pH without

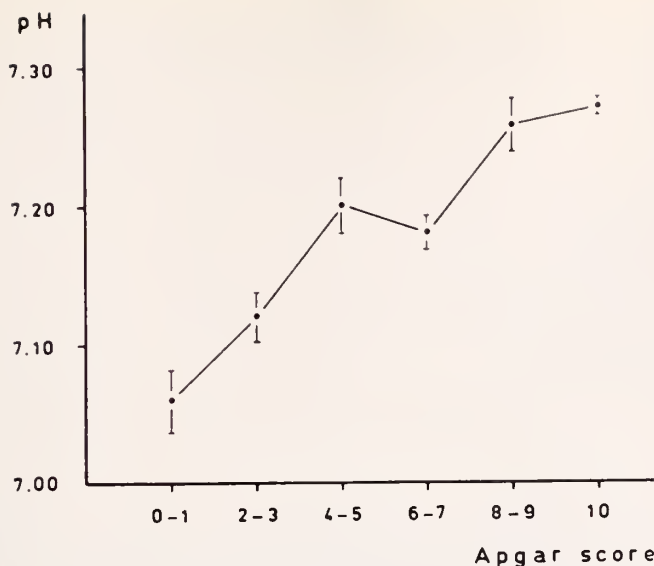


FIG. 9. Mean pH values for paired Apgar scores. Vertical bars represent \pm S.E.

any change in the fetal heart rate. In one case early in the series, when the value of fetal blood studies was not appreciated by a colleague and intervention was withheld, the pH was observed to fall from 7.13 to 6.89, when the heart stopped. During this time, the fetal heart rate was carefully counted at 5 minute intervals, was always regular and at between 120 and 150 beats per minute, and no meconium was seen. Such cases are rare, and fortunately tachycardia or bradycardia usually give good warning that the state of the fetus needs investigation.

This technique adds to the work of the obstetric staff, and we have problems with staff shortages in Britain. If it is to be adopted for routine work in large units, certain questions must be asked:

(1) *To which cases should it be applied?* Obviously it could not, and should not, be applied to every case. We have used it in all cases with clinical signs that suggest fetal distress. Secondly, it has been used in cases with possible placental insufficiency, especially in those cases in which the fetus was "small for dates," and cases of toxæmia, postmaturity, antepartum haemorrhage, or those with a previous history of intrauterine death. I am indebted to Dr. Richard Beard for Tables IV and V, which are based on a half year's deliveries. It is shown that in a sample of 1968 cases, clinical fetal distress occurred in 100 out of 169 "at risk" cases (59 percent), but in only 196 out of 1799 "normal" cases (11 percent). It is also shown that if there were signs of fetal distress, then acidæmia was found about twice as often in the "at risk" cases as in the other cases.

It is reassuring to a clinician that in this series acidæmia was not found in the "at risk" cases that gave no clinical evidence of fetal distress; however,

TABLE IV
Fetal Blood Sampling for "At Risk" Patients

	No.	No. with Subsequent Clinical Fetal Distress	No. with Acidaemia
Preeclampsia.....	84	52	14
Postmaturity.....	23	12	1
Preeclampsia and postmaturity.....	13	10	2
Elderly primigravidae.....	19	9	3
"Small for dates" and oligohydramnios.....	16	5	1
Poor obstetric history.....	5	5	2
Antepartum haemorrhage.....	6	5	0
Long labour.....	3	2	0
Total.....	169	100	23

TABLE V
*Total Number of Patients Delivered, 1968**
Fetal Blood Sample Collected in 364 Cases (22%)

Patients Thought to be Normal who Developed Clinical Signs of Fetal Distress	"At Risk" Patients (169)	
	With Clinical Signs of Fetal Distress	Without Clinical Signs of Fetal Distress
196	100	69
Acidaemia	Acidaemia	Acidaemia
22	23	0

* Excluding infants dying from congenital malformation or Rhesus incompatibility.

there were at least two cases in this subgroup in which the discovery of acidaemia preceded the clinical signs.

(2) *Can fetal blood sampling in early labour predict whether distress will occur in late labour, or exclude it?* This is certainly not possible. All that a sample shows is the state of the fetal blood at the time it is collected.

(3) *Will fetal blood sampling reduce perinatal mortality?* In Queen Charlotte's Hospital, which accepts many abnormal cases, the perinatal mortality rate was 27 per thousand in 1963, and 29 per thousand in 1964. Since fetal blood sampling has been used freely, the rate has fallen slightly, to 22 per thousand in 1967, and 23 per thousand in 1968. These gross figures mean little, but if fetuses weighing less than 2000 grams, and cases of congenital malformation or Rhesus incompatibility are excluded, the perinatal mortality for the remaining cases has fallen by about a third. In all fairness, it must be said that there has been a national fall in perinatal mortality, and it is possible that the improvement is partly due to closer supervision of the cases studied.

In our present department at King's College Hospital, we intend, through

TABLE VI

Year	C S Rate	No. of C S	No. of C S For Fetal Distress			S B and N N D*
1962	6.7	196	40			21
1963	6.6	206	40			21
1964	7.9	242	41			20
				Clinical F D Alone	Clinical F D with Acidaemia	
1965	5.9	193	36	19	17	6
1966	5.8	186	16	4	12	16
1967	4.9	157	11	3	8	10

* Excluding infants less than 2,000 gm, congenital abnormalities, and Rhesus incompatibility.

the generosity of the Wates Foundation, to set up an "intensive care unit" for the "at risk" fetus, especially the "small for dates" fetus. The intention is to watch these patients well during pregnancy, with such procedures as oestriol estimations, amniocentesis, and frequent hospital admission; to monitor their course during labour, both by sampling and by the use of cardiac ratemeters; and to cooperate with the paediatricians in their postnatal supervision. So far, there have been too few studies in which fetal blood sampling has been followed through by blood sampling in the neonatal period. It is too much to hope that all this will make a tremendous difference to perinatal mortality, because prematurity, obstetric trauma, placental and cord accidents will still take their toll, and the large problem of congenital malformation remains. We hope, however, to eliminate many of the hypoxic deaths, and our National Perinatal Survey of 1958 showed how numerous these are.

(4) *Will fetal blood sampling give a better assessment of the need for operative delivery?* This seems to be its greatest contribution, especially in preventing unnecessary Caesarean section. Table VI shows that there has been a reduction in the number of sections for fetal distress, with no increase in perinatal mortality.

Lack of oxygen may be only one aspect of fetal distress. It is well known that the fetus or newborn infant can survive periods of asphyxia that would be fatal in older children. Fetal anaerobic glycolysis will continue to provide energy until so much lactic acid has been formed that the pH of the blood falls to 6.9, when glycolysis is inhibited (40).

The infant who is "small for dates" because of maternal hypertension or placental disease, or even if no explanation is found, has a higher perinatal mortality than a normal-sized infant, and Drillien (41, 42) has shown that these undersized infants are more likely to suffer from neurological disorders. It is to these infants that special attention should be given, and in this fetal blood sampling has a part to play. It might assist us to investigate disorders

of carbohydrate or amino acid metabolism, or of potassium balance. We can also assess the hormonal response of the fetus to the stress of labour, and the effect of drugs. At this point, it would be possible to begin a second, but more speculative, lecture.

We may ask whether fetal anaerobic glycolysis ultimately fails because of exhaustion of carbohydrate reserves, and in this field Dr. Shelley of Oxford has contributed much (43-45). She has shown that in many species of animals there is a relationship between survival times during asphyxia and cardiac reserves of glycogen. Villee (46) states that the glycogen concentration in fetal human cardiac muscle is ten times greater than in adult cardiac muscle. The brain has a low glycogen reserve, and depends on supplies of glucose reaching it after mobilization from the liver glycogen (47). The liver glycogen concentration of the fetus reaches the adult level by midpregnancy, and rises to twice that level in the last month. Fetal skeletal muscle also has a high concentration of glycogen, but this probably contributes little to the blood glucose. In human fetuses observations can only be made on autopsy material, and although most of this comes from infants that have died from asphyxia, all the available evidence supports the animal experiments. The premature infant is at a disadvantage, with lower carbohydrate reserves, and it is of especial interest that low reserves were found in "small for dates" fetuses (48).

All this suggests that exhaustion of the carbohydrate reserves may cause fetal death, but in fact death during labour or soon afterwards occurs before the reserves are fully depleted, because accumulation of lactic acid inhibits glycolysis. However, intrauterine carbohydrate deficiency may be related to neonatal hypoglycaemia, especially in the "small for dates" infant, and this in turn to neurological abnormalities (49, 50), the risk of which may be reduced by treatment with alkali and glucose.

In cases of severe fetal distress, whether from hypoxia or from carbohydrate deficiency, tissue damage occurs and intracellular potassium is released so that the serum concentration rises, but present evidence does not suggest that this is the cause of fetal death.

We return, therefore, to the overriding importance of the assessment of fetal hypoxia in practical obstetric management. Criticism of the minutiae of technique, or of the physiological significance of fetal blood sampling does not detract from its value in the elucidation of the unreliable signs of fetal distress, and it is a method of investigation with many yet untried applications in research. I am convinced that Dr. Rubin would have approved of its use for both clinical work and research.

Acknowledgment

I am very grateful to Dr. Richard Beard for allowing me to make so much use of his published work in this lecture, and to the Journal of Obstetrics and Gynaecology for permission to reproduce Figures 6-9.

References

1. Prystowsky, J.: Bull Hopkins Hosp 10:1, 1958.
2. Chung, F., and Hon, E. H.: Obstet Gynec 13:633, 1959.
3. Smyth, C. N.: Proc Roy Soc Med 11:1253, 1968.
4. Hon, E. H.: Amer J Obstet Gynec 75:1215, 1958.
5. Caldeyro-Barcia, R., Méndez-Bauer, C., Posiero, J. J., Escarcena, L. A., Pose, S. V., Bieniarz, J., Arnt, I., Gulm, L., and Althabe, O.: In *The Heart and Circulation in the Newborn and Infant*, Cassels, D. E., ed. Grune and Stratton, New York 1966.
6. Smyth, C. N.: J Obstet Gynaec Brit Comm, 72:920, 1965.
7. Day, E., Maddern, L., and Wood, C.: Brit Med J 4:422, 1968.
8. Coltart, T. M., Trickey, N. R. A., and Beard, R. W.: Brit Med J 1:342, 1969.
9. Dawes, G. S.: Proc Roy Soc Med 61:1227, 1968.
10. Acheson, G. H., Davies, G. S., and Mott, J. C.: J Physiol (London) 135:623, 1957.
11. Dawes, G. S., Mott, J. C., and Shelley, H. J.: J Physiol (London) 146:295, 1959.
12. ———, and Mott, J. C.: J Physiol (London) 170:524, 1964.
13. Campbell, A. G. M., Cockburn, F., Dawes, G. S., and Milligan, J. E.: J. Physiol (London) 192:111, 1967.
14. Friedman, E. M., Gray, M. J., Gynfogel, M., Hutchinson, D. L., Kelley, W. T., and Plentl, A. A.: J. Clin Invest 29:622, 1960.
15. Daniel, S. S., Adamsons, K., and James, L. S.: Pediatrics 37:942, 1966.
16. Blechner, J. N., Meschia, G., and Barron, D. H.: Quart J Exp Physiol 45:60, 1960.
17. Meschia, G., Battaglia, F. C., and Barron, D. H.: Quart J Exp Physiol 42:163, 1957.
18. Dancis, J., Worth, M., and Schneidau, P. M.: Amer J Physiol 188:535, 1957.
19. MacRae, D. J.: Proc Roy Soc Med 61:490, 1968.
20. Nyberg, R., and Westin, B.: Acta Physiol Scand 39:216, 1957.
21. Panigel, M.: Amer J Obstet Gynec 84:1664, 1962.
22. Hellman, L.: Amer J Obstet Gynec 94:687, 1966.
23. Rivard, G., Motoyama, E. K., Acheson, F. M., Cook, C. D., and Reynolds, E. O. R.: Amer J Obstet Gynec 97:925, 1967.
24. Motoyama, E. K., Rivard, G., Acheson, F., and Cook, C. D.: Lancet 1:286, 1966.
25. Moya, F., Morishima, H. O., Schnider, S. M., and James, L. S.: Amer J Obstet Gynec 91:76, 1965.
26. Saling, E.: Arch Gynaek 197:108, 1962.
27. Morris, E. D.: Proc Roy Soc Med 61:487, 1968.
28. Kubli, F.: Europ Congr Perinatal Med, 1968 (in press).
29. Teramo, K.: Europ Congr Perinatal Med, 1968 (in press).
30. Browne, A. D. H.: Europ Congr Perinatal Med, 1968 (in press).
31. Beard, R. W.: Proc Roy Soc Med 61:1247, 1968.
32. James, L. S., Weisbrot, I. M., Prince, C. E., Holaday, D. A., and Apgar, V. A.: J Pediat 52:379, 1958.
33. Seligman, S. A.: Proc Roy Soc Med 61:491, 1968.
34. Kirschbaum, T. H.: Lying-In 1:325, 1968.
35. Kubli, F.: In *Fetale Gefahrenzustände und ihre Diagnose*, Thieme, Stuttgart, 1966.
36. McDonald, J. S.: Amer J Obstet Gynec 97:912, 1967.
37. Beard, R. W., and Morris, E. D.: J Obstet Gynaec Brit Comm 72:496, 1965.
38. Saling, E.: Z Geburtsh Gynaek 161:262, 1963.
39. Beard, R. W., Morris, E. D., and Clayton, S. G.: J Obstet Gynaec Brit Comm 74:812, 1967.
40. Dawes, G. S., Mott, J. C., Shelley, H. J., and Stafford, A.: J Physiol (London) 168:43, 1963.
41. Drillien, C. M.: Pediatrics 39:238, 1967.
42. ———: Hosp Med 1:937, 1967.

43. Shelley, H. J.: Brit Med Bull 17:137, 1961.
44. ———: Brit Med J 1:273, 1964.
45. ———: J Obstet Gynaec Brit Comm 76:1, 1969.
46. Villee, C. A.: Cold Spr Harb Symp Quart Biol 19:186, 1954.
47. Stafford, A., and Weatherall, J. A. C.: J Physiol (London) 153:457, 1960.
48. Shelley, H. J., and Neligan, G. A.: Brit Med Bull 22:34, 1966.
49. Neligan, G. A., Robson, E., and Watson, J.: Lancet 1:1286, 1963.
50. Drage, J. S., and Berendes, H.: Pediat Clin N Amer 13:635, 1966.

Received for publication April 24, 1969

Tolbutamide in Pregnancy and Diabetes

HENRY DOLGER, M.D., JOHN J. BOOKMAN, M.D., AND CHARLES
NECHEMIAS, M.D.

Since a significant number of diabetic women being treated with tolbutamide are of child-bearing age, it is important to obtain information on the efficacy of this agent in controlling the diabetes during pregnancy, and on the possible teratogenic effects of the drug and its influence on perinatal survival rates. Diabetic women receiving any oral hypoglycemic agent are usually transferred to insulin therapy as soon as pregnancy is discovered. However, many women who conceive while taking oral hypoglycemic drugs are not immediately aware that they are pregnant, or do not report that fact to their physicians for several weeks or even months, and these women are therefore receiving these agents during perhaps the most crucial time of their pregnancy. In addition, at The Mount Sinai Hospital Prenatal Clinic, 5 percent of all patients are discovered to have an abnormal glucose tolerance at some time during their pregnancy. Some of these women, and many known diabetics previously managed on diet alone, will require a hypoglycemic agent for satisfactory control of their diabetes as pregnancy progresses.

This paper reports the course and outcome of 97 pregnancies in 76 diabetic women who received tolbutamide some time in their pregnancy during the decade from 1957 to 1967; further studies were discontinued in 1967 because of Food and Drug Administration restrictions on the use of oral hypoglycemic agents during pregnancy. We have had no experience with oral hypoglycemic agents other than tolbutamide; other workers have reported their findings with several other drugs (1).

Onset and Duration of Therapy

Forty of the 97 pregnancies studied occurred in women who received tolbutamide during the first trimester of pregnancy. Twenty-six of these pregnancies occurred in women who were taking the drug at the time of conception. The remaining 14 women were either known diabetics who were managed on diet alone prior to pregnancy, but who required hypoglycemic therapy to control their diabetes during the early weeks of pregnancy (Class B diabetics), or were patients whose diabetes was initially discovered during the pregnancy, and who would therefore have been considered Class A diabetics by the classification of Priscilla White (2), were it not for the fact that they, too, required hypoglycemic therapy for control of their hyperglycemia and glycosuria, and must therefore also be classified as Class B. Therapy with tolbutamide was maintained in these 40 pregnancies for from 16 to 36 weeks;

From the Department of Medicine and the Prenatal Diabetic Clinic of The Mount Sinai Hospital, New York, N.Y. 10029, and Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

27 of the pregnancies were managed with tolbutamide until the time of delivery.

Tolbutamide therapy was confined to the second and third trimesters in the remaining 57 pregnancies, all of which occurred in clinic patients who were initially seen at a later stage of pregnancy than were our private patients; 42 of these pregnancies have been previously reported by the authors (3). The drug was administered for 2 weeks or less in 18 of these pregnancies; in 8 pregnancies it was administered for 3 to 4 weeks; in 14 pregnancies the drug was used for from 5 to 8 weeks; and in the remaining 17 pregnancies, the drug was given for 9 to 26 weeks.

Control of Diabetes

The dose of tolbutamide used in all pregnancies ranged from 0.5 to 3 gm daily; the majority of patients received daily doses of from 1 to 2 gm. In 21 instances, progressively increasing hyperglycemia and glycosuria could not be controlled by tolbutamide, and insulin therapy became necessary, usually in the third trimester. In 74 patients, however, tolbutamide provided satisfactory control of the diabetes throughout pregnancy, and the patients were receiving the drug at the time of delivery. In the remaining 2 patients, there was sufficient amelioration of the diabetes toward the end of pregnancy to permit discontinuation of the tolbutamide, and these women were receiving no hypoglycemic medication at the time of delivery.

Fetal and Neonatal Loss

Six of the 97 pregnancies resulted in stillbirths. One of the stillbirths occurred in the 32nd week of gestation, one in the 36th week, two in the 37th week, and one each in the 38th and 39th weeks. Two occurred in patients whose diabetes was known before the pregnancy, two in patients who had been Class A diabetics in a previous pregnancy but were not known to be diabetic between pregnancies, and two occurred in patients first discovered to have diabetes during the current pregnancy. Tolbutamide had been administered in a dosage of from 0.5 to 2 gm daily for a period of from 2 to 22 weeks; in three instances it had been started in the second trimester and continued until delivery, and in three patients it was not begun until the third trimester. The autopsies of all six macerated fetuses revealed no congenital anomalies.

One neonatal death occurred 18 hours after delivery of a 2025 gm baby by Caesarian section in the 36th week of gestation. The mother was a Class B diabetic of 4 years duration who had been managed by diet alone until the 30th week of pregnancy, when 1 gm of tolbutamide was added to achieve satisfactory control of the diabetes. At that time, the mother was also considered to have essential hypertension, and by the time of delivery, superimposed preeclampsia. Autopsy of the baby revealed atelectasis and hyaline membrane disease; no congenital anomalies were reported.

Congenital Anomalies

The major concern over the use of any oral hypoglycemic agent during pregnancy has been the question of possible teratogenicity. Of our 97 pregnancies in patients receiving tolbutamide, 3 resulted in babies with congenital anomalies discovered at birth. These 3 cases will be described in detail:

Case 1. A mongoloid infant with congenital heart disease was delivered vaginally at 36 weeks gestation to a Class B mother with known diabetes of 5 years duration, who had been managed on diet alone until the 12th week of pregnancy, when tolbutamide in a dose of 1 gm daily was begun. The tolbutamide was continued in a daily dose of either 0.5 or 1 gm until the time of delivery.

Case 2. An infant with a patent ductus arteriosus was delivered vaginally at 36 weeks to a mother who was first discovered to have diabetes in the fourth week of her pregnancy, and who was placed on 1 gm of tolbutamide at that time, and maintained on that dose throughout the pregnancy.

Case 3. An infant with a sixth digit on one hand was delivered vaginally following induction of labor in the 36th week of gestation to a Class B mother who had been taking 2 gm of tolbutamide and 50 mgm of phenformin daily at the time of conception and until the 26th week of pregnancy, when she first reported that she was pregnant. At that time, the phenformin was discontinued, and the patient managed on 2 gm of tolbutamide alone for the remainder of the pregnancy.

Summary and Conclusion

In our experience with 97 pregnancies during which tolbutamide was taken by the mother, the drug was successful in controlling the diabetes in 74 instances; in 21 pregnancies, hyperglycemia and glycosuria could not be controlled with tolbutamide, and insulin therapy was necessary in the last trimester.

The combined fetal and neonatal loss rate in tolbutamide-treated pregnancies was 7.2%, which parallels the rate of 6.8% in the general experience of The Mount Sinai Hospital Prenatal Diabetes Clinic with Class B diabetics treated with insulin (4).

The incidence of congenital anomalies of 3.1% compares favorably with the varied estimates of frequency for congenital defects in the babies of diabetic mothers in general (5).

It is our feeling, therefore, that tolbutamide is effective in managing diabetes in many pregnant women who require some form of hypoglycemic therapy, and that its use is not associated with an increased incidence of perinatal mortality or congenital anomalies.

References

1. Jackson, W. P. U., Campbell, G. D., Notelovitz, M. B., and Blumsohn, D.: Tolbutamide and Chlorpropamide during Pregnancy in Human Diabetics, *Diabetes* 11:Suppl. 1962.

2. White, P.: Pregnancy Complicating Diabetes, *Amer J Med* 7:609, 1949.
3. Dolger, H., Bookman, J. J., and Nechemias, C.: Diagnostic and Therapeutic Value of Tolbutamide in Pregnant Diabetics, *Diabetes*, 11:Suppl, 1962.
4. ———, ———, and ———: The Management of Diabetes in Pregnancy, *J Mount Sinai Hosp NY* 30:479, 1963.
5. Kyle, G. C.: Diabetes and Pregnancy, *Ann Intern Med* 59:Suppl 3, 1963.

Received for publication March 31, 1969

Cardiac Transplantation in Man: Its Therapeutic and Other Importance*

DENTON A. COOLEY, M.D.†

Introduction to the Arthur Master Lecture

BY ROBERT S. LITWAK, M.D.

Arthur, we gather here tonight to honor you at the annual Arthur Master Lecture, supported by a fund provided by your many friends.

Dr. Arthur Master worked his way through high school and college; he graduated from Cornell University Medical College in 1921. After interning and spending several years at The Mount Sinai Hospital, Dr. Master was awarded a traveling fellowship from Cornell University Medical College; he worked with Sir Thomas Lewis in London on experimental studies of heart block. Dr. Master's career has been punctuated by a number of contributions which have gained him international renown. He was one of the first to emphasize the dangers of being overweight in patients with heart disease. Almost 40 years ago, Dr. Master developed the then startling concept that patients often made a complete functional recovery after heart attacks, and should be advised to return to work and resume reasonably normal physical activities. Dr. Master was one of the first to show that subendocardial infarction could, and frequently does occur in the absence of coronary occlusion. There are so many other contributions, truly too numerous to mention. Certainly, the exercise test which now bears his name, the so-called two step test, is used throughout the world as a means of validating the existence of coronary artery disease.

Dr. Master has had a distinguished military career, starting as a humble apprentice in the First World War, and rising to the rank of Navy Captain in the Second World War. By actual count, Arthur is a member of 30 professional societies, and over the years he has been privileged to preside over a number of these.

He is the author of over 400 articles, including six text books. Dr. Master serves on the editorial board of eight medical journals, and in between all this somehow manages to conduct a busy cardiology practice. This vigorous scholar is a member of Phi Beta Kappa, and has been the recipient of a number of honors recognizing his contributions to medicine, including the Jacobi Medal from The Mount Sinai Hospital, the Gold Medal of Honor from the American College of Chest Physicians, and an Award for Distinguished Achievement from the New York Academy of Medicine. This past year, the Journal of Modern Medicine presented him its Distinguished Achievement Award—to quote—"in recognition of your meticulous and extensive studies of the functional capacity of the human heart in disease, and development of useful clinical criteria for diagnosis and treatment."

Many cardiovascular procedures have been evolved over the years which adequately correct or palliate cardiac lesions of various types. Replacement of malfunctioning components of the human heart has been successfully accomplished in numerous cases, but until December 3, 1967, total cardiac replacement was only an experimental operation confined to laboratory animals. Since Barnard's first attempt on that date, transplantation of the human heart has been proven feasible clinically in over a hundred subsequent trials;

* Presented as the Arthur Master Lecture, March 18, 1969, The Mount Sinai Hospital, New York, N. Y. 10029.

† Professor of Surgery, Baylor College of Medicine; Physician in Chief, Texas Heart Institute of St. Luke's-Texas Children's Hospitals, Houston, Texas.

TABLE I
Indication for Operation in Cardiac Transplant Recipients

Disease	No. of Patients
Coronary artery disease.....	13
Rheumatic multivalvular disease	1
Endocardial fibroelastosis; myocardiopathy.....	1
Myocardiopathy.....	1
Complete A-V canal; pulmonary hypertension.....	1
	17

the ability of an allografted heart to support human circulation has been established. Salvage of patients with end-stage heart disease unresponsive to conventional treatment is now possible, but the problems involved in cardiac transplantation, such as procurement of donors, recognition and control of rejection, the role of leukocyte antigens, and infection enhanced by immunosuppressive drugs, still await solutions. At the Texas Heart Institute, we have performed 18 cardiac transplants in 17 patients, plus 1 xenograft using a sheep's heart. An infant who received a combined cardiopulmonary transplant, and a man who underwent retransplantation when his first allograft was rejected after nearly 7 months, are included in this series.

Advanced occlusive disease of the coronary arteries has been the indication for operation in most of our patients (Table I). These were patients with severe angina and/or intractible cardiac failure, for whom conventional procedures of myocardial revascularization held a prohibitive risk. In one case, rheumatic valvular disease, usually correctable by valve replacement, was the indication for transplant since the disease was very severe, involving aortic, mitral, and tricuspid valves. Two patients with myocardiopathy (one, a child with endocardial fibroelastosis) received allografts, but further application of cardiac transplantation in patients with myocardiopathy may be discouraged by recent speculation that the autoimmune factors which destroyed the original heart might similarly affect an allograft. Complete atrioventricularis communis, together with pulmonary hypertension, pneumonia, atelectasis, and pulmonary infarctions was the diagnosis in an infant who received the heart and lungs of an anencephalic donor. Certain other congenital defects such as aortic atresia, mitral atresia, or hypoplasia of the ventricle could be considered for transplantation when the disease is in a terminal stage, since other techniques at present are unavailing in such cases. Primary cardiac tumors with extensive cardiac involvement may also be amenable only to cardiac transplantation. The therapeutic advantages of cardiac allografting are limited in patients with preexisting multiple organ disease that would not be helped by improved cardiac function, or in patients with diabetes which would be aggravated by steroids used for immunosuppression. Systemic infection or neoplasia are definite contraindications. A recipient's age is sometimes relevant to the decision for or against operation, and psychological adaption should

TABLE II
Cause of Cerebral Damage in Transplant Donors

Cause of Death	No. of Patients
Intracranial hemorrhage	7
Trauma	6
Brain tumor	2
Encephalomalacia	1
Anencephaly	1
	—
	17

be considered, but these factors must be weighed according to the individual situation. The urgency of a recipient's condition, and the availability of a donor influence each case in varying degrees.

Irreversible cerebral damage (confirmed by atonia, fixed and dilated pupils, areflexia, apnea, and isoelectric EEG), and absence of cardiac abnormalities or transmissible disease were the requirements observed in selection of donors. Spontaneous hemorrhage, trauma, and tumor were the most common causes of death (Table II).

Transplantation is scheduled when cardiopulmonary function of the donor fails. Under cardiopulmonary bypass, using a disposable bubble oxygenator primed with 5 percent dextrose in water, the recipient's heart is excised with both ventricles, all valves, and portions of the atria with both atrial appendages attached. Posterior walls of the atria with both vena cava and pulmonary veins remain in place to permit anastomosis of the donor heart (Fig. 1), which has been excised simultaneously in an adjacent operating room. The donor heart, previously anticoagulated with heparin, is removed by opening the posterior left atrium between the orifices of the pulmonary veins, ligating the superior vena cava, and incising the right atrium from the inferior vena cava toward the right auricular appendage. The sinoauricular node and most of its internodal conduction pathways to the atrioventricular node are preserved by this technique (Fig. 2). The unperfused, normothermic donor heart is inserted by continuous suture anastomoses of the atria, progressing from left to right (Figs. 3 and 4), the main pulmonary arteries, and the aortae (Figs. 5 and 6). Following aspiration of intracardiac air with a needle and syringe and release of the aortic cross clamp, coronary flow is restored, and cardiac action returns in either sinus rhythm or ventricular fibrillation. Fibrillation is easily converted to sinus rhythm by a direct current countershock. Digitalis, or sometimes, isoproterenol, may be required for stable postoperative cardiac function. The patient is removed to an isolated recovery room, where physiologic functions are monitored continuously.

Through a collaborative study with Dr. Paul Terasaki, each donor/recipient pair is tissue typed and matched according to: (1) ABO red cell compatibility; (2) lymphocyte crossmatch for preformed antibodies; and (3) lymphocyte antigen match (Terasaki's grading scale: A-F). Tissue match

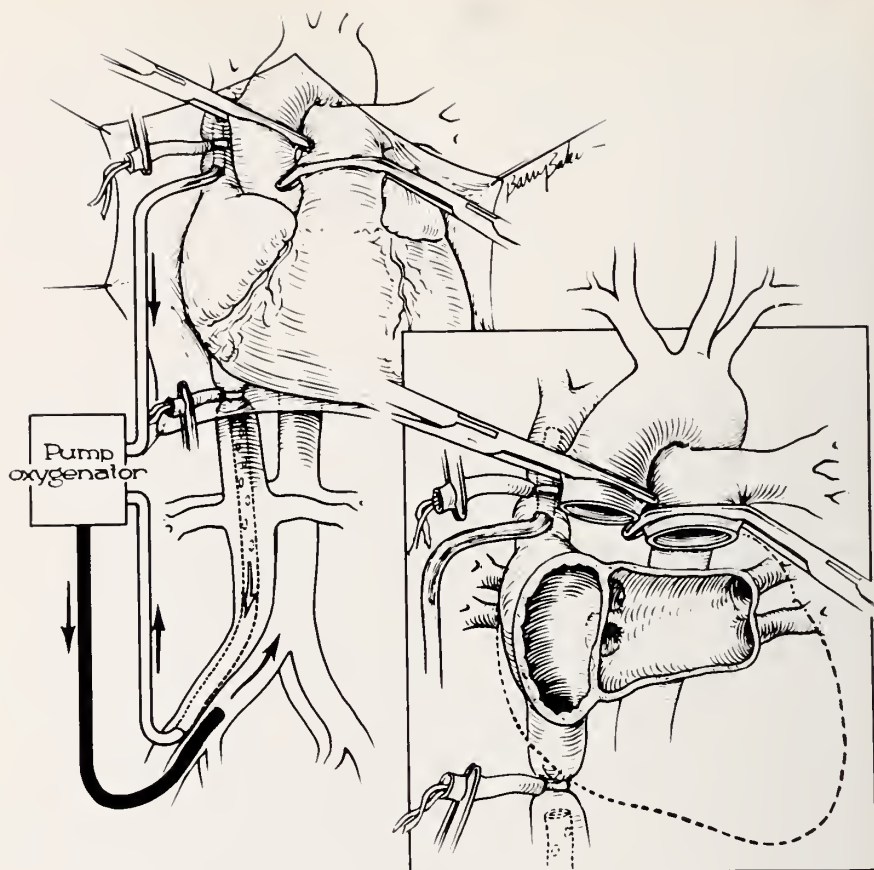


FIG. 1. Technique of cannulation for cardiac transplantation. Inferior caval catheter may be inserted through right atrium (inset). Portions of atria and great vessels remaining after excision of heart (reprinted by permission from Cooley, D. A., Bloodwell, R. D., and Hallman, G. L.: Cardiac Transplantation for Advanced Acquired Heart Disease, *J Cardio Surg* 9:403-413, 1968).

grade in this series ranged from D to C plus, with an average grade of C minus.

Our immunosuppressive program is derived from that used by Starzl et al for renal allografts, and consists of the administration of azathioprine, corticosteroids, and antilymphocytic globulin (ALG). Our patients were the first cardiac transplant recipients to receive ALG. This medication, prepared from horse antihuman thymocyte serum, contributes to suppression of rejection while permitting lower dosages of azathioprine and corticosteroids.

In each case function of the allograft was adequate to maintain circulation of the recipient, and each left the operating room in good condition. In most patients, this was followed by improved status and ambulation in the first postoperative week. Three patients were able to leave the hospital, and two

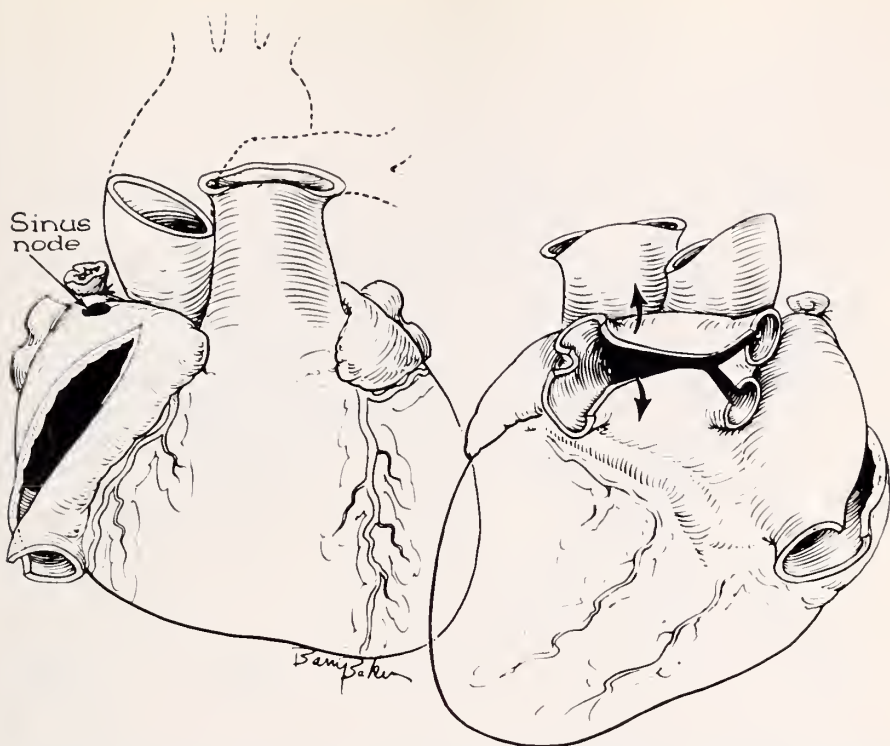


FIG. 2. Preparation of donor heart for transplantation. Incision in right atrium extends from inferior vena cava into appendage, avoiding S-A node. Left atrium opened posteriorly with incisions connecting pulmonary veins (reprinted by permission from Cooley, D. A., Bloodwell, R. D., and Hallman, G. L.: Cardiac Transplantation for Advanced Acquired Heart Disease, *J Cardio Surg* 9:403-413, 1968).

became gainfully employed. Serial cardiac catheterization performed in several patients showed that cardiac indices were within normal range during the first month after operation. An increase in rate, cardiac output, and stroke index was noted in the transplanted hearts following exercise, but the increase was smaller and slower in onset than in control patients. A sinus mechanism originating in the S-A node of the transplanted heart was observed in each recipient. Nodal rhythm has not occurred.

A total of 14 patients have died, 6 in the early postoperative period. One of these, a man with a probable allergy to the horse serum in ALG, died of sepsis, leukopenia, and gram negative bacterial pneumonia. Another died of preexisting renal and hepatic failure 8 days after operation. Acute rejection caused three deaths (two of these were in patients with myocardiopathy) (Table III). At autopsy, the donor hearts of these patients revealed increased weight, hyperemia, scattered hemorrhagic areas, diffuse interstitial edema, and round cell infiltration. The cardiopulmonary transplant recipient died of pulmonary insufficiency 14 hours after operation.

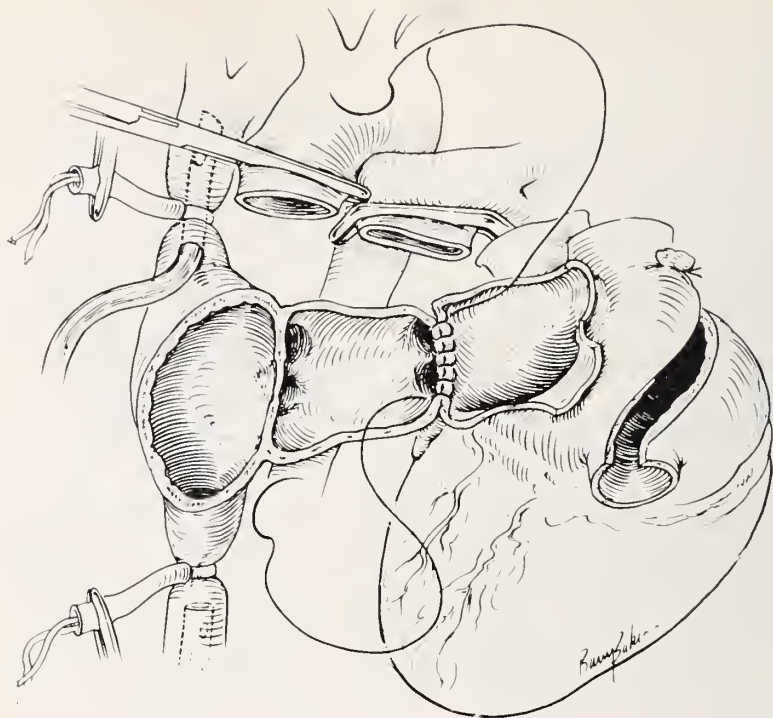


Fig. 3. Donor heart reversed and placed in pericardial sac. Suture line begins at left border of left atria and is completed at atrial septum of recipient (reprinted by permission from Cooley, D. A., Bloodwell, R. D., and Hallman, G. L.: Cardiac Transplantation for Advanced Acquired Heart Disease, *J Cardio Surg* 9:403-413, 1968).

Late deaths occurred in eight patients at 6½ weeks to 6⅔ months after operation. Three of these deaths were due to infection. One woman developed a wound infection due to *Serratia marcescens* at the site of femoral artery cannulation, and died of thrombocytopenia and hemorrhage from a duodenal ulcer 55 days posttransplant. Massive herpetic infection, pneumonia, and sepsis caused the death of a 50-year-old man 9 weeks after operation. Another man died of *Pseudomonas pneumonia* 6½ weeks after transplantation. Of the five patients who died of chronic rejection, one survived 6⅔ months, until irreversible rejection of his first allograft developed. He underwent retransplantation, but died 36 hours later. The patient who received the xenograft in a desperate attempt at salvage, died on the operating table of hyperacute rejection.

From May 1968, to May 1969, 42 other patients were considered for cardiac transplantation, but did not undergo operation because compatible donors were not available. Nineteen of these patients died during the first month of the waiting period, and another eight died between the second and fourth months.

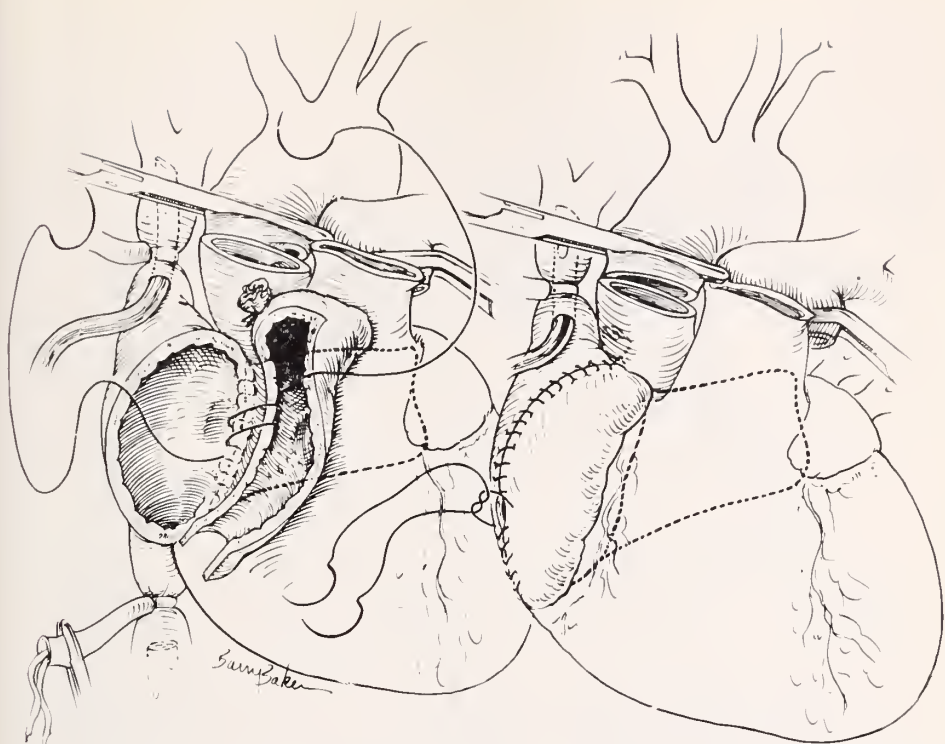


FIG. 4. Anastomosis of right atria begins at atrial septum of recipient and is completed laterally (reprinted by permission from Cooley, D. A., Hallman, G. L., Bloodwell, R. D., Nora, J. J., and Leachman, R. D.: Cardiac Transplantation as Palliation of Advanced Heart Disease, Arch Surg (to be published)).

Three transplant recipients are alive today, at 2 weeks, 4 months, and 8 months after transplantation. The patient who has survived 8 months has the highest tissue match grade (C plus), and has experienced no episodes of rejection.

The correlation reported in renal transplantation between histocompatibility and incidence of rejection has also been observed in our cardiac allografts. Noteworthy, was presence of a definite increase in mean survival time and decrease in the number of rejection episodes for patients with C matches, as compared to those with D matches.

Although better long-term results for cardiac transplant recipients will depend on improvements in tissue matching and immunosuppressive therapy, the therapeutic value of the procedure in appropriate cases has been demonstrated. Moreover, in addition to its therapeutic advantages, the cardiac transplant program has had other far-reaching significance. It precipitated the questionings which led to a new, and more logical, definition of death. The earlier medical and legal decision that death occurred only when cardiac func-

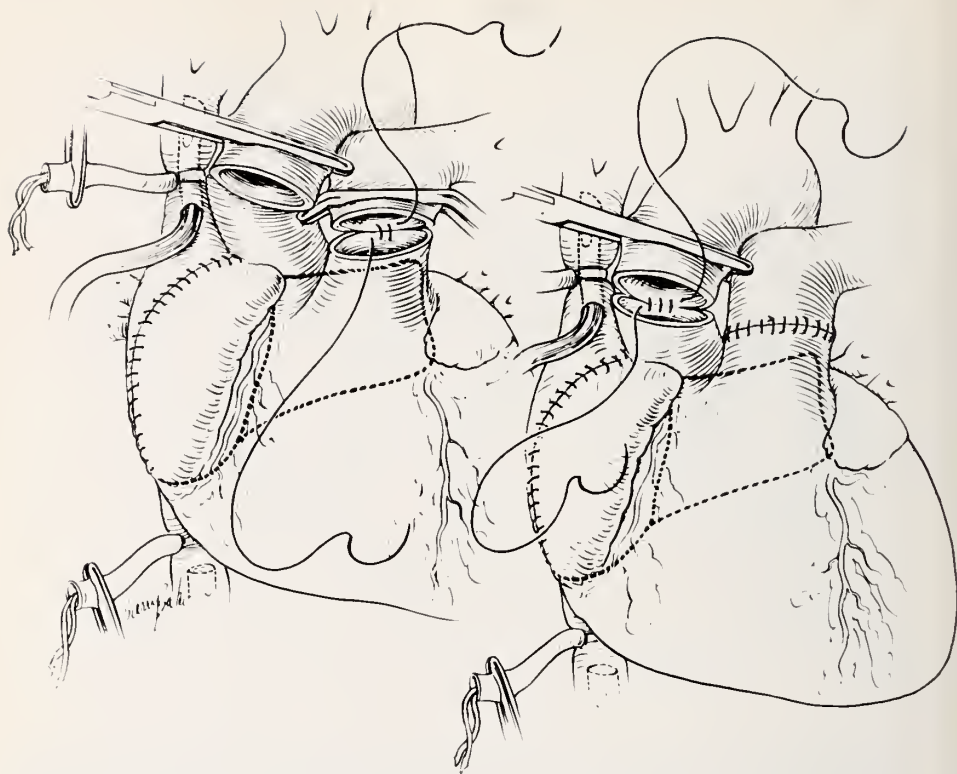


FIG. 5. Pulmonary artery and aorta anastomosed with continuous suture (reprinted by permission from Cooley, D. A., Hallman, G. L., Bloodwell, R. D., Nora, J. J., and Leachman, R. D.: Cardiac Transplantation as Palliation of Advanced Heart Disease, *Arch Surg* (to be published)).

tion ceased was recognized as unsatisfactory, since heart action can often be maintained indefinitely in a patient who has suffered irreversible cerebral destruction. With the advent of cardiac transplantation, a use was found for this viable heart, which was pumping to no avail in the presence of brain death, but could save the life of another patient dying of heart disease. Surgeons demanded that the question, "what is death?," be unequivocally settled, and, urged to immediate deliberation, the medical and legal professions finally established a conclusive definition. Irreversible brain damage, even when other organs including the heart remain viable, is now accepted as constituting a patient's death.

The cardiac transplant program also acted as a strong educational influence, since its successful utilization depended on dispersing the cloud of superstition surrounding the heart with a persistent aura of romanticism. The public was forced to reexamine its tenacious beliefs about the mythical properties of the heart as a source of emotions, personality traits, and the very soul of an individual.

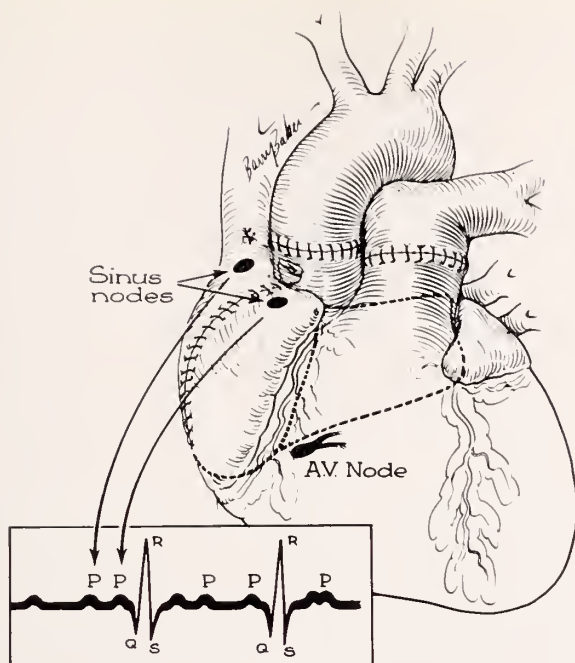


FIG. 6. Anastomoses completed and cannulae and clamps removed. Patient has two S-A nodes and each produces a P wave in the ECG. Only the P wave from the S-A node in the donor heart is followed by a ventricular contraction (reprinted by permission from Cooley, D. A., Hallman, G. L., and Bloodwell, R. D.: *Transplantation of the Heart*, In *Craft of Surgery*, Cooper, P., ed. Little, Brown, and Company, Boston, Mass. (to be published)).

TABLE III
Cause of Death in Cardiac Transplant Recipients

Cause of Death	No. of Patients
Chronic rejection.....	5
Infection.....	4
Acute rejection.....	3
Preexisting diseases.....	1
Pulmonary insufficiency.....	1
	—
	14

Cardiac transplantation has opened new fields of investigation in immunology, biology, and cellular biology. Various areas of research which had reached an impasse have been stimulated afresh, now accelerating along paths which could lead to an understanding of many currently obscure diseases.

Moreover, the knowledge gained from the transplant program, that a cardiac allograft can support human circulation, and that the denervated allograft

reacts sluggishly to influences which cause increase or decrease in cardiac output, has injected new life into the projects geared to developing a satisfactory mechanical cardiac replacement, and makes that possibility more attainable.

In closing, let me express to Dr. Arthur Master and the founders of this lectureship my sincere appreciation for the honor of being selected to deliver this lecture. Dr. Master has inspired many young men during his illustrious career, and I am proud to be in his and your presence on this occasion.

Received for publication June 10, 1969

Cardiac Arrhythmias due to Hypersensitivity: A Report of Ten Cases

JOSEPH HARKAVY, M.D.†

Cardiac arrhythmia due to hypersensitivity, characterized by premature contractions, ventricular extrasystoles, paroxysmal tachycardia, and atrial fibrillation, both paroxysmal and recurrent, may be present in patients with normal hearts, and occasionally in some with diseased hearts.

In a study of 9,950 patients, Kissane, Brooks, and Clart (1) found 361 or 3.6% of cases with supraventricular tachycardia, of which 122 or 34% occurred in persons without heart disease. Out of 175 cases with paroxysmal supraventricular tachycardia in a study by Hejtmancik, Herrman, and Wright (2) 44 of 25% had no evidence of heart disease.

That atrial fibrillation, most frequently of the paroxysmal as well as the more established type, may also occur in the absence of demonstrable organic heart disease in about 6.5% of cases, has been reported by a number of cardiologists: Fowler and Baldrige (3); Orgain, Wolff, and White (4); Phillips and Levine (5); Master and Eichert (6); and others. Brill (7), in a follow-up of one case for over 11 years, found convincing proof that overwork from uncontrolled atrial fibrillation may by itself produce cardiac enlargement and congestion in a heart otherwise free of organic disease. Similar opinions were expressed by Mohler and Lintgen (8).

Discussion in the literature as to the underlying causes of premature beats, ectopic tachycardia, and atrial fibrillation in normal hearts are characterized by broad generalizations. Digestive and emotional disturbances, fatigue, exertion, alcoholism, coffee, tobacco, and disease of the biliary tract are regarded as playing roles in precipitating these arrhythmias. The mechanisms involved, however, are varied and need clarification.

The finding of cardiac arrhythmias in certain allergic patients with normal hearts, associated at times with hay fever or asthma, suggested the possibility that these cardiac disturbances may have been due to hypersensitivity.

Pathological and Physiological Observations

That the heart in man may be the seat of reactions characterized by various types of arrhythmias due to sensitization, finds support in the fundamental observations of the cardiac response in the course of anaphylaxis in the experimental animal and man.

Electrocardiographic abnormalities during acute anaphylaxis in guinea pigs, dogs, and rabbits have been described by various authors as consisting of bradycardia and tachycardia preceded by extrasystoles, depressions in the S-T segments, QRS complexes, and T waves, as well as heart block (Auer and

† Clinical Professor of Medicine (Emeritus), Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

Lewis (9), Auer and Robinson (10), Criepp (11), and Mikulicich (12)). These responses were attributed to spasms of muscles of the coronary vessels resulting in anoxemia of the heart muscle, and due to contraction of the arterioles of the lungs leading to permeability changes in the tissues. However, working with isolated hearts obtained from sensitized animals, Kellner, Penna, and Schweid (13), Harkavy and Perlman (14), as well as Feigen et al (15) demonstrated that the heart *per se* participates in the process of sensitization, and is capable of responding directly to antigenic impact independently of any alterations in coronary blood flow. Kellner and his colleagues showed that perfusion with homologous antigen of the isolated heart, which had been previously sensitized in the usual manner to proteinase and other agents, causes disturbance in impulse formation and conduction in the form of ectopic beats and AV block of varying degree. Similar changes were obtained when isolated atrial muscle, devoid of blood supply, was exposed to the specific sensitizing agent. Most recently, cardiac changes in guinea pigs sensitized through the mucous membrane of the digestive tract by the introduction of crystalized ovalbumin into the stomach by a probe, were reported by Majovic, Andjukovic, and Djordjevic (16). Electrocardiographic abnormalities were demonstrable in the isolated heart by perfusion according to the Langendorff (17) method *in vitro*, and also *in vivo* after preadministration of antigen by gastric probe, or intravenously. The authors concluded that sessile antibodies are also fixed to the myocardium during sensitization through the mucous membrane of the digestive tract.

Feigen (15) and his coworkers have demonstrated that the response of the sensitized guinea pig heart to perfusion with an effective dose of homologous antigen (ovalbumin) was found to consist of an acceleration of the rate of the heart beat, an increase in amplitude of contraction, and a decrease in coronary flow. The characteristic mechanical response of the isolated atria was an increase in amplitude and frequency of contraction, the most intense effect of which resulted in fibrillation. These abnormalities were brought about by the release in the perfusate of physiologically active material elaborated during the anaphylactic reaction, identified as histamine by pharmacological methods, as well as by paper chromatography of butanolic extracts. All of the mechanical and electrical events noted in the Langendorff heart and the isolated atria could also be reproduced precisely by an appropriate dose of histamine. That histamine can induce paroxysmal atrial tachycardia through direct stimulation of the rabbits sinoauricular node, has also been shown by Levi and Giotto (18).

Clinical Observations

The clinical counterpart of the effect of histamine on the heart is illustrated by two cases described by Rosenfeld, Silverblatt, and Grishman (19). In one instance, a 51-year-old allergic white male with a past history of asthma at the age of 17, since then fully controlled, was admitted to the hospital in 1955 for an elective gastrectomy because of a duodenal ulcer. Following injection of 0.5 mg of histamine diphosphate prior to a Rhus test meal, the patient

went into shock, and experienced severe precordial pain with marked electrocardiographic changes characterized by RST depressions in the standard and precordial leads, with significant generalized T wave changes. Administration of 1 cc of adrenalin and 50 mg of Benadryl® intravenously resulted in complete recovery with return of the electrocardiogram to normal. Two days later, a subtotal gastrectomy was successfully performed.

The second patient, who developed a severe asthmatic attack following ingestion of aspirin for pain, went into shock within 20 minutes, which was controlled with epinephrine, intravenous aminophyllin, and eoramine. An electrocardiogram taken shortly after the initial response to therapy revealed abnormally tall P waves in Leads II and III; aVF and deep wide notched Q wave in V3. Administration of ACTH completed the recovery of the patient. These manifestations were interpreted by the authors as sequential to the release of endogenous histamine. However, the mechanism involved in the aspirin sensitivity is not yet fully established.

Case Reports

The present communication deals with a group of ten patients, nine of whom had no demonstrable evidence of heart disease, who manifested various types of cardiac arrhythmia characterized by extrasystoles, supraventricular tachycardias, and atrial fibrillation. In some of these patients the cardiac arrhythmia appeared as the only manifestation of allergy, implying that the major shock organ was the heart, whereas in others, the arrhythmia was associated either with respiratory symptoms, such as asthma various gastrointestinal disturbances in the form of gaseous distention and diarrhea or urticaria and dermatitis, suggesting involvement of multiple shock organs. A more detailed exposition of the past history and clinical course of the arrhythmia in these patients is as follows:

PAROXYSMAL TACHYCARDIA, EXTRASYSTOLES

Case 1. M.I., aged 10, was first seen in 1965. He had a childhood history of asthmatic attacks after respiratory infections. At the age of 5, he developed a serum sickness type of reaction following administration of Madribon® after a tonsillectomy. In 1963, when he was 8 years old, he began to manifest intermittent attacks of paroxysmal tachycardia (Fig. 1). Allergy studies dis-

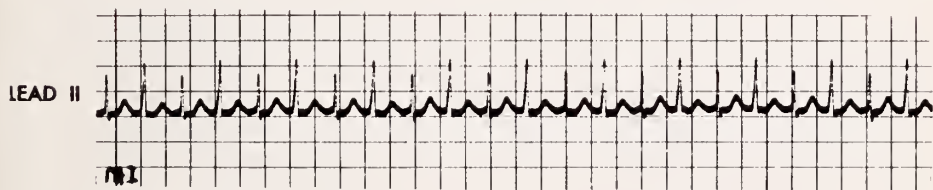


FIG. 1. Case 1. M.I., aged 10. Supraventricular tachycardia with electrical alternans after ingestion of chocolate and milk.

closed that he was sensitive to chocolate, milk, orange, apple, dust, and pollens of trees and grasses. Further investigation disclosed that these attacks were most marked during the grass pollen season, after the ingestion of milk together with chocolate or apples. Shorter paroxysms occurred after eating cheese, or when he inhaled dust. Elimination of the incriminating foods, and hyposensitization to pollens and dust abolished the attacks. As he grew older, he began to outgrow his milk allergy, and now, at the age of 15, he can drink a glass of milk a day without any cardiac symptoms. He still gets mild attacks of paroxysmal tachycardia after inhaling dust.

Case 2. A.H., aged 32, was first seen in 1964. One brother has asthma. She herself had a history of hay fever and pollen asthma for many years. She manifested ventricular extrasystoles for 9 years. Alcoholic beverages of all kinds and tobacco induced asthmatic attacks, and accentuated the arrhythmia. During the ragweed season of 1963, after drinking wine combined with various allergenic foods unknown to her, she suffered a syncopal attack and paroxysmal tachycardia.

Allergy studies revealed positive skin reactions to tree, grass, and ragweed pollens, molds, tobacco, and numerous foods. The most important of the latter proved, after repeated provocative clinical trials, to be wheat, milk, rye, corn, and soya bean. Rye caused diarrhea and numerous extrasystoles. Challenge with an intradermal test with corn extract during the ragweed season of 1968 precipitated a paroxysmal attack of tachycardia, rate of 170. After eliminating the incriminating foods and pollen hyposensitization, her pulse has been perfectly normal for the past 5 years. An intercurrent bladder infection would precipitate a return of the extrasystoles. Treatment with antibiotics controlled the bladder condition with disappearance of the extrasystoles.

Case 3. B.H., aged 10, the daughter of A.H. (Case 2). Her father has hay fever, and had been subject to attacks of tachycardia. When seen in 1965, she gave a history of urticaria and severe epidermophytosis. She had been subject to attacks of paroxysmal tachycardia, rates of 160–180, since 1963, in the spring and fall during the pollen season. In between attacks the heart was perfectly normal. Allergy studies showed that the patient reacted to chocolate, Coca Cola, orange, dust, and the pollens of trees, grasses, and ragweed. Provocative tests with chocolate and/or orange precipitated attacks of tachycardia. Their elimination has resulted in complete freedom from tachycardia during the past 4 years.

Case 4. J.H., aged 5, son of A.H. (Case 2), developed hives and paroxysmal sinus tachycardia, rate of 170, after eating chocolate. Skin reaction to chocolate was positive. Avoidance of chocolate has prevented recurrences of tachycardia.

Case 5. R. R., aged 33, was first seen in 1964. He had no personal family history of allergy. He suffered from attacks of paroxysmal tachycardia after smoking and drinking alcohol and coffee for 11 years. Paroxysmal tachycardia appeared 24 hours after imbibing alcoholic drinks such as beer, whiskey, or cognac. These he had eliminated. An immediate severe cardiac response followed

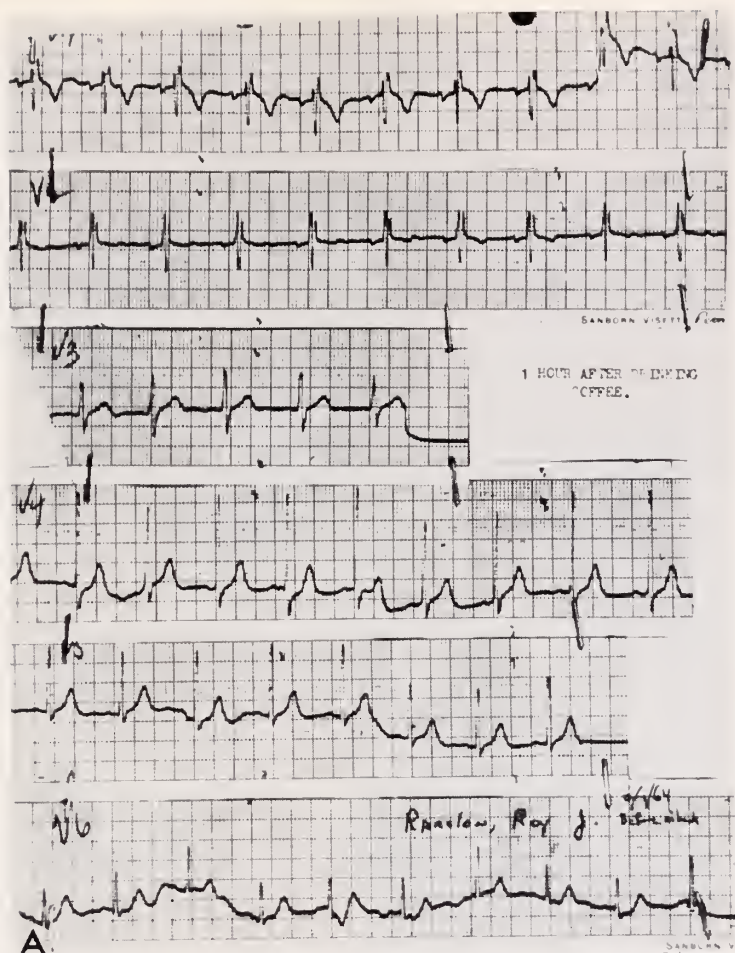
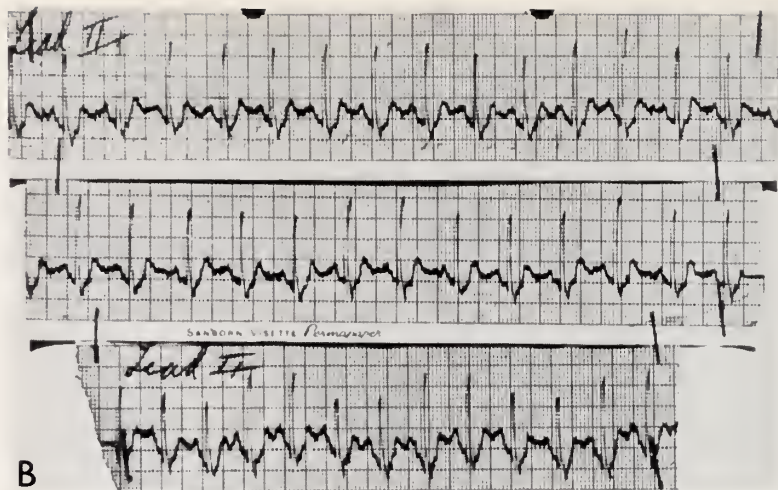


FIG. 2A. Case 5. R.R., aged 33. Right bundle block 1 hour after drinking coffee. Coffee allergy.

the drinking of two cups of coffee. This was indicated electrocardiographically by paroxysmal tachycardia, RBB block, and coronary insufficiency. The reaction was controlled by a subcutaneous injection of 1 cc Benadryl® within 10 minutes (Figs. 2A, 2B, and 2C). This suggested that the attack was not due to caffeine, but to allergy to the proteins of coffee.

Case 6. D.L., was first seen in September 1967. She gave a history of hay fever and asthma for 30 years during the grass pollen season, without ever having been immunized against these pollens. She also sustained attacks of paroxysmal tachycardia, not only after ingestion of specific foods such as chocolate, milk, and orange, but also after exposure to cat hair. Skin tests for these allergens were positive. A visit to the home of a friend who had a cat induced itching of the eyes and lacrimation, followed by a strong chill during



Tochycardia, Shartness of Breath, and Fasciculations

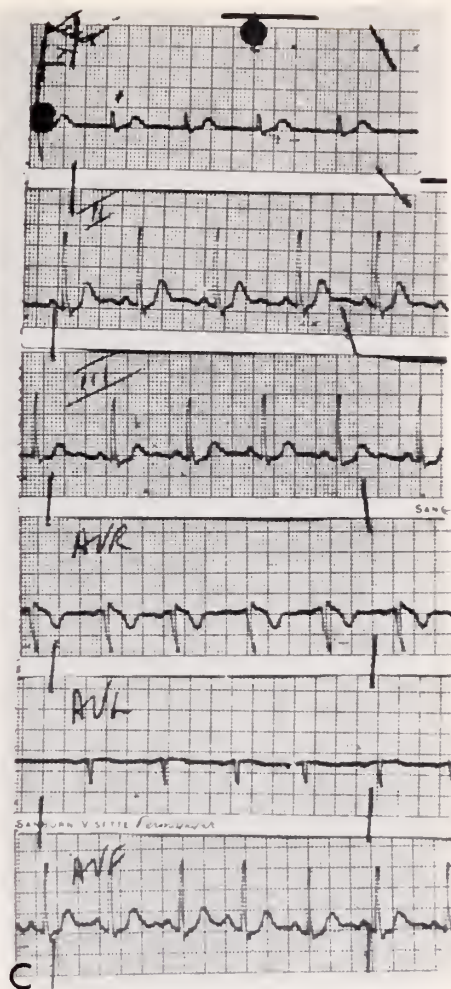
FIG. 2B. Case 5. R.R., aged 33. Coffee allergy. Sinus tachycardia. ST depressions.

that night and a severe attack of tachycardia. Challenge by a subcutaneous injection of cat hair extract by her physician resulted in an attack of tachycardia, rate 150, within 15 minutes. Avoidance of exposure to cats and the incriminating foods have completely abolished her attacks of tachycardia to date.

ATRIAL FIBRILLATION

Case 7. B.G., male, aged 48, came for observation in May 1963. Family history disclosed that his father had eczema. He suffered intermittently with precordial pain and atrial fibrillation for 8 years, especially during the summer months. His attacks continued for 3 to 4 days in succession every 1 or 2 months, and were most severe after smoking and ingestion of various foods, especially shell fish and spices during the pollen season in April and May, requiring hospitalization of 7 to 10 days. There was a distinct correlation between some of the foods which he suspected to be responsible for his symptoms and the positive skin tests. Although he also gave marked cutaneous reactions to tree, grass, and ragweed pollens, he never had any signs of hay fever. After the cardiac arrhythmia was controlled in May 1963 by the elimination of the incriminating foods, he developed severe hay fever for the first time in his life in June 1963, which continued throughout the grass and ragweed pollen season of 1963, and had to be treated with steroids. In other words, there was a shift in the shock organ from the heart to the respiratory system. In the latter part of 1963, he also had three attacks of fibrillation: one after inhaling camphor present in a bale of old clothes; another after absorption of menthol contained in cough lozenges; and a third after inhaling turpentine when his apartment was painted. In the spring of 1964 he had a attack of atrial fibrillation due to tree pollen, for which he had not been protected. Now he is being hyposensitized to the pollens of trees, grasses, and ragweed, dust, and molds, and

FIG. 2C. Case 5. R.R., aged 33. Coffee allergy. Tachycardia has disappeared. Record returning to normal.



10 min after Benadryl, 10 mg, given IM.

has eliminated the offending foods. He has not had an attack of atrial fibrillation since 1964 to date (1969) (Fig. 3).

Case 8. H.G., aged 59. Her mother has asthma. In 1963, she developed angioedema of the tongue after eating shell fish. She experienced occasional attacks of precordial pain and tachycardia, on and off for 4 years, which proved on examination to be atrial fibrillation. During the years of 1962-1964, she had similar daily attacks. To control the latter, she was treated by her physician with Quinidine, which precipitated purpura. She was therefore referred for allergy studies. Skin tests disclosed a number of positive reactions to foods. After evaluating these reactions, it was found that some were clinically significant, and others not. It was finally established by clinical trial and the process of elimination that orange, tomatoes, eggs, milk, and coffee were re-

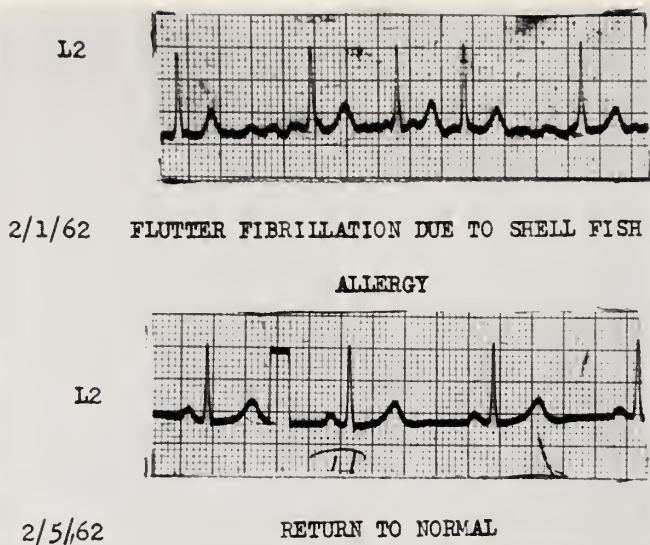


FIG. 3. Case 7, B.G., aged 48.

sponsible for the attacks of atrial fibrillation. A sinus or a throat infection also precipitated an attack of cardiac arrhythmia. These were controlled with suitable antibiotics. Since excluding the incriminating foods, the patient has been completely free of atrial fibrillation since 1965.

Case 9. B.K., male, aged 55, was first seen in October 1962. He gave a history of cough and asthma during July and August for 11 years, which were treated symptomatically by his physician. In November 1962, while under his care, he developed severe asthma after a respiratory infection. A similar episode occurred in December 1963, which terminated in status asthmaticus. On both occasions, the pulmonary symptoms were associated with atrial fibrillation and signs of coronary insufficiency. Treatment with antibiotics and steroids controlled the asthma and the cardiac arrhythmia. Subsequent electrocardiograms were normal. Allergy studies disclosed that he was sensitive to various foods, dust, pollens of trees, grasses, and ragweed, as well as molds to which he was exposed in his occupation as a handler of vegetables. Hyposensitization against the incriminating inhalants and omission of some foods to which he was allergic, as determined by clinical trial, has resulted in control of the asthma to a large extent, without a single recurrence of fibrillation since 1964. He shows a moderate amount of pulmonary fibrosis and some emphysema as a consequence of his long standing inadequately treated asthma. Because of prolonged use of steroids administered for a number of years by his physician, which is being gradually reduced, he has hypertension of 180/100 and a Cushingoid facies. His heart, however, showed no clinical or electrocardiographic evidence of disease up to March 1969. Exacerbations of asthmatic attacks after a respiratory infection are now readily controlled with antibiotics and a small increase in steroids.

Case 10. In contrast to the cases described above, whose arrhythmia occurred in patients with normal hearts, is that of patient T.P. She was first seen at the age of 57 and gave a history of recurrent attacks of urticaria, angioedema, and colitis for many years. Allergy studies disclosed that she was sensitive to shell fish and milk products. At the age of 68, after eating a mixture of lobster and oyster followed by ice cream, she developed a severe attack of fibrillation with VPC confirmed electrocardiographically. This subsided within 24 hours. A follow-up electrocardiogram indicated ST and T wave changes indicative of myocardial damage. On subsequent occasions, whenever she ate shell fish, she experienced attacks of angina pectoris and cardiac arrhythmia, characterized by premature beats alternating with angioedema. This was relieved by catharsis. She finally stopped eating shell fish and lived to the age of 74, when she died of a virus pneumonia.

Discussion

A review of the clinical course of 9 of the 10 cases reported herewith indicates that premature ventricular beats, paroxysmal tachycardia, and atrial fibrillation may occur on the basis of hypersensitivity in healthy individuals with normal hearts, and without any demonstrable cardiac disease. These arrhythmias may appear in allergic subjects after ingestion of specific foods or inhalants, such as dust and pollens. Superimposed hypersensitivity to some exciting agent may also account for arrhythmia in older allergic individuals with diseased hearts, as exemplified in Case 10 this group.

The allergic origin of cardiac arrhythmia is established on the basis of criteria used in the identification of the common allergic syndromes, i.e.: (1) The presence of a family or personal history of allergy; (2) the incidence of respiratory or other vascular allergic manifestations, such as urticaria or angioedema; (3) the demonstration of positive skin reactions; (4) the verification of the relationship between the reacting foods or inhalants and the cardiac symptoms by repeated clinical trials; and (5) the complete cessation and control of the arrhythmia by removal and hyposensitization with the offending allergens.

Studies dealing with patients who developed extrasystoles and paroxysmal tachycardia due to food allergy, the exclusion of which caused a disappearance of the clinical manifestations, have been reported previously by Harkavy (20), Weil (21), Laubry and Mussio-Fournier (22), Luria and Wilensky (23), Davidson, Thoroughan, and Bowcock (24), and Kern (25). Atrial fibrillation in a patient with tuberculosis, due to hypersensitivity to para-aminosalicylic acid, has also been described by Hubaytar and Simpson (26).

Allergic individuals who develop cardiac arrhythmia behave very much like asthmatics in whom paroxysms of asthma may be evoked, not only by polyvalent sensitivity to various extrinsic factors as well as intrinsic, such as infection, but also occasionally by emotional stress, both conscious and unconscious. It is therefore quite conceivable that the sensitized myocardium of a hypersensitive individual which reacts in the form of arrhythmia, may also respond in a similar manner following an emotional crisis.

Since most of the patients sensitive to pollens and foods had their attacks of arrhythmia during the pollen season after ingestion of specific foods and simultaneous exposure to pollens or other inhalants to which they were not protected, there is a possibility that the abnormal cardiac reactions may have been accentuated by the synergistic action of pollen and allergenic foods, or other inhalants. This is best illustrated in patient B.G. (Case 7), who was sensitive to pollens and foods, and had most of his episodes of atrial fibrillation during the pollen season, due to food allergy. When the pollen season was over he could eat with impunity some of the foods which had precipitated attacks during the pollination period.

Symptomatic control of the acute paroxysms of arrhythmia was achieved by the oral or subcutaneous administration of antihistaminics such as Benadryl® (diphenhydramine hydrochloride), 50 mg. The more severe attacks were controlled by the ingestion of 50 mg of Benadryl® combined with a tablet of Actifed® (tripolidine hydrochloride and pseudoephedrine hydrochloride), or one tablet of Tedral® (theophyllin 130 mg, ephedrine hydrochloride 24 mg, phenobarbital 8 mg).

Summary

It is suggested that the cardiac symptoms in the ten patients under discussion were the result of an immediate antigen-antibody reaction in the myocardium, with a release of histamine similar to that observed experimentally in the sensitized isolated heart by Feigen et al. This is supported by the fact that antihistaminics, as indicated above, usually controlled the attacks. The favorable effects of Tedral® or Actifed® may possibly be explained by the observations of Lichtenstein and Margolis (27), who found that the catecholamines and methylxanthines inhibit the release of histamine *in vitro*.

A delayed form of hypersensitivity following an intercurrent infection was also regarded as playing a role in the precipitation of attacks of arrhythmia in Cases 2, 8, and 9. The character of the arrhythmia in these patients was exactly the same as that evoked by food and inhalants. Treatment with antibiotics controlled both the infection and the arrhythmia. In Case 9, whose atrial fibrillation was associated with infective asthma, the administration of antibiotics combined with steroids terminated both conditions.

The prophylactic treatment of arrhythmia in these patients was accomplished by the elimination of the specific allergenic excitants, and hyposensitization with pollens and inhalants.

In view of these findings, it would seem advisable that patients with normal hearts who manifest arrhythmia of unknown origin be investigated from the point of view of hypersensitivity, even in the absence of a family or personal history of allergy, i.e., Case 5. Episodes of cardiac arrhythmia may also occasionally occur in constitutionally allergic patients with diseased hearts, due to superimposed allergy to foods or drugs, the elimination of which is followed by disappearance of the arrhythmia. It is therefore suggested that arrhythmias

proved to be due to sensitization be designated, "Cardiac Arrhythmias due to Hypersensitivity."

Acknowledgment

I wish to express my appreciation to Doctors Eli Wallack, Sidney Simon, Emile Somekh, Hyman Levy, and Sanford Stein for referring these patients for investigation.

References

1. Kissane, R. W., Brooks, R., and Clart, T.: Relation of Supraventricular Paroxysmal Tachycardia to Heart Disease and Basal Metabolism, *Circulation* 1:950, 1950.
2. Hejtmancik, M. R., Herrman, G. R., and Wright, J. C.: Paroxysmal Supraventricular Tachycardia Complicating Organic Heart Disease, *Amer Heart J* 56:671, 1958.
3. Fowler, W. M., and Baldrige, C. W.: Auricular Fibrillation as the Only Manifestation of Heart Disease, *Amer Heart J* 28:311, 1944.
4. Orgain, E. S., Wolff, L., and White, P. O.: Uncomplicated Auricular Fibrillation and Auricular Flutter: Frequent Occurrence and Good Prognosis in Patients without Other Evidence of Cardiac Disease, *Arch Intern Med* 57:493, 1936.
5. Phillips, E., and Levine, S. A.: Auricular Fibrillation without Other Evidence of Heart Disease, *Amer J Med* 7:478, 1949.
6. Master, A. M., and Eichert, H.: Functional Paroxysmal Auricular Fibrillation, *Amer J Med Sci* 211:336, 1946.
7. Brill, I. C.: Congestive Heart Failure Arising from Uncontrolled Auricular Fibrillation in the Otherwise Normal Heart, *Amer J Med* 2:541, 1947.
8. Mohler, H. K., and Lintgen, C.: Auricular Fibrillation: An Analysis of 220 Cases, *Penn Med J* 35:68, 1931.
9. Auer, J., and Lewis, P. A.: Physiology of the Immediate Reaction of Anaphylaxis in the Guinea Pig, *J Exp Med* 12:151, 1910.
10. ———, and Robinson, C. C.: An Electrocardiographic Study of the Anaphylactic Rabbit, *J Exp Med* 18:450, 1913.
11. Criepl, L. H.: Electrocardiographic Studies of the Effect of Anaphylaxis on the Cardiac Mechanism, *Arch Intern Med* 48: 1098, 1931.
12. Mikulicich, G.: Electrocardiographic Changes in Experimental Anaphylactic Reactions, *Allergy* 22:249, 1951.
13. Kellner, A., Penna, M., and Schweid, A. J.: Cardiac Anaphylaxis, *Circulation* 12:670, 1955.
14. Harkavy, J., and Perlman, E.: Tobacco Allergy in Coronary Disease, *Ann NY Acad Sci* 68:327, 1960.
15. Feigen, G. A., Vaughan-Williams, E. M., Peterson, J. K., and Nielsen, C. B.: Histamine Release and Intracellular Potentials during Anaphylaxis in the Isolated Heart, *Circ Res* 8:713, 1960.
16. Majovic, M., Andjukovic, I., and Djordjevic, P.: Cardiac Changes in Guinea Pigs Sensitized through the Mucous Membrane of the Digestive Tract, *Acta Allerg* 23:205, 1968.
17. Langendorff, O.: Untersuchungen am Überlebenden Säugethierherzen, *Arch Ges Physiol* 61:291, 1895.
18. Levi, R., and Giotto, A.: Effect of Histamine in Sinoatrial Node Cells of Rabbit Heart, *Experientia* 23:66, 1967.
19. Rosenfeld, I., Silberblatt, M. L., and Grishman, M. D.: Allergic Shock in Humans with Electrocardiographic Findings, *Amer Heart J* 53:463, 1957.
20. Harkavy, J.: Cardiac Arrhythmias with Special Reference to Paroxysmal Tachycardia:

- Auricular Fibrillation and Premature Beats in Constitutionally Allergic Individuals, *J Mount Sinai Hosp NY* 5:273, 1938.
21. Weil, O.: Tachycardie Paroxystique et Anaphylaxie, *Presse med* 40:368, 1932.
22. Laubry, C., and Mussio-Fournier, J. C.: Tachycardie Paroxystique d'Origine Anaphylactique, *Bull Soc Med* 49:404, 1925.
23. Luria, R., and Wilensky, I.: Kann die paroxysmale Tachycardie als eine Allergische Krankheit gelten, *Deutsch Med Wschr* 56:1430, 1930.
24. Davidson, H. M., Thoroughan, J. C., and Bowcock, H.: Cardio-Vascular Allergy, *Southern Med J* 3:560, 1945.
25. Kern, J.: Discussion; Is Allergy a Factor in Angina Pectoris?, *J Allerg* 4:67, 1932.
26. Hubaytar, R. T., and Simpson, D. G.: Atrial Fibrillation due to Hypersensitivity to Para-Aminosalicylic Acid, *Amer Rev Resp Dis* 86:773, 1962.
27. Lichtenstein, L. M., and Margolis, S.: Inhibition by Catecholamines and Methylxanthines, *Science* 161:902, 1968.

Received for publication March 31, 1969

The Psychiatrist Looks at Medical Progress*

M. RALPH KAUFMAN, M.D.†

The medical profession has always stood for maintenance of health and treatment of illness. The fact that it progresses and creates problems should not in any way be interpreted as arguing for limitations.

We seem to be preoccupied with a multitude of problems, all of which relate in one way or another to medical advances. The population explosion is an excellent example, in a sense, of what has been building over a period of many years. The name of Malthus epitomizes such concern in the early 19th century. At that time, there was relatively little that medicine could do of a positive nature that would lead to a "dangerous increase in population." Progress in medicine at all levels has now made this a seething reality. One brief example is the eradication of malaria in Ceylon, which is usually referred to as a prime example. You eradicate malaria, and the population increases three and fourfold and presents a world with all kinds of problems. I should like to emphasize that I am discussing the problems and not making a value judgment as to whether or not the eradication of malaria is a desirable goal.

The recent brilliant contributions to the field of genetics, typified by DNA and RNA, have led to a great deal of discussion and concern in many areas. The possibility of man's control over genetics has been hailed on one hand as a major potential triumph, and on the other has been feared as a potential for robbing the world.

Another area relating to problems of over-population is the creation of The Pill. This, as you well know, has led to ferment and turmoil since it involves conflicting mores, ethical and religious beliefs, some aspects of basic personality structure, attitudes towards the family, and the need for children. It is those aspects of the problems that are our major interest.

Medicine recognizes some of the physiological side effects which are of great concern, and which probably play some role in the adversary positions in regard to this whole problem of contraception, but they are not necessarily pertinent to our discussion today.

Availability of The Pill in many instances has nothing whatsoever to do with its use. Studies indicate that for psychological and emotional reasons, many women have either not accepted The Pill, nor follow the necessary routine.

The conscious wish for family planning or contraception may actually be negated by unconscious needs. In some individuals, the biological need of a woman for children makes it impossible for them to use contraceptive devices.

* Presented at a Symposium on Medical Ethics, The Hadassah Medical Organization, February 3, 1969.

† Esther & Joseph Klingenstein Professor of Psychiatry; Chairman, Department of Psychiatry, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029.

Some people need to live for the day, and the function of the reality principle in terms of the future may play no role for them. Some variations of existentialism tend in that direction.

There are many other examples of controversial areas that might be discussed if time permitted. Medical progress by its very nature involves people, and today's cultural climate is such that the "right to know" is of paramount importance; it is taken for granted that no human subject should be utilized unless there is "informed consent." This was an issue in the Geneva Conference of 1964, and was specified in detail in the Declaration of Helsinki, 1964.

There is no question about the need for such consent. The problem arises in relation to what "informed consent" really means, and whether this is ultimately possible.

In an experiment in which a number of individuals were divided into two groups, half of them were thoroughly briefed on the nature of this experiment and its hazards, and the other half were accepted as volunteers without such briefing. It turned out that there seemed to be no ultimate differences between the informed and the uninformed as to the nature of the experiment (1).

Recent experimental work in the area of perception indicates clearly what the sages have always known—we hear what we want to hear, and do not hear what we do not want to. In addition, especially in the area of double blind experiments, "informed consent" may contaminate the total experiment.

There have been new techniques developed for the induction of abortion. The procedure under hospital conditions is generally conceded to carry minimal risk. Whether there has been progress or regression in this field to a great extent has to do with attitudes towards the whole problem of abortion, rather than with technical innovations.

In the United States today there is a spectrum of opinion which runs from the feeling that abortion is a purely personal matter which should be available to any woman who wants it, to extremely strict laws which limit the availability of abortion to the point where it is legally almost unavailable.

In today's mail two pamphlets were received from the Association for the Study of Abortion. One was the program of an international congress entitled "Abortion in a Changing World," in which the following topics were discussed: ethical aspects; medical aspects; legal aspects; social aspects; and the global aspects of abortion, with panel sessions on abortion and poverty; abortion and public health; abortion and obstetrics; and abortion and mortality. In each of these topics the psychological and emotional problems are present, and in many instances may be the dominant factors. The Newsletter of this organization reported on the conference in which some 150 participants and observers, representing 20 nations and every major geographic area, met in November 1968 for 3 days at the Homestead in Hot Springs, Virginia. Attention is drawn to two opposing statements in this report as made by two Catholic priests. One, a Jesuit philosopher, Joseph F. Doneeel, denies that abortion is immoral in the early stages of pregnancy, "because the embryo is certainly not a human being" at that time. He added that this was the position of the Catholic

Church for several centuries which it abandoned because of erroneous scientific information. On the other hand, Father Granfield argues for the immediate infusion of the human soul when the ovum is fertilized by the sperm. He rests his case on the most recent advances of biology, the DNA theory, which holds that the "fertilized zygote has the genetic identity of the adult at conception." The reason I cite these statements is to emphasize that at the core of most of the conflicts lie certain religious beliefs.

In the light of such complex attitudes, one can readily see that abortion for any specific individual may be fraught with tremendous psychological trauma. Psychiatrists are familiar with patients who have reacted with great guilt and psychiatric symptomatology. On the other hand, there are also situations where the interruption of pregnancy has been accepted without such reactions.

There is also the era of emphasis on instantaneous communication, as shown by a heart transplant in South Africa which is known throughout the world before the patient leaves the operating room. Within a relatively short period of time a hundred or more heart transplants have taken place. Kidney transplants from live donors or cadavers are almost an old story by now. Liver transplants have been reported in the medical literature. Prosthetic replacements of arteries have been successfully completed on any number of individuals.

There are many technical and biological problems that still exist, but it is almost taken for granted that with time these problems will be solved. Therefore, it seems as though eventually the solution to these problems will permit superb technical procedures.

The problems relating to these advances, however, are psychological, emotional, and social. Man was created in God's image and has been concerned about his body since the time of creation.

The human body is more than an integrated system of parts that function until worn out. Man's relationship to his body is an exceedingly complex one. Indeed, not only the psychoanalyst considers that basic personality development is related to body and body function. Myth, legend, and modern psychology indicate that the body as a whole, and its parts, have a unique, deep, psychological, and symbolic significance. This is true not only for the external body, but for its internal organs as well, as they exist in fact and fantasy.

The heart was, and still is, considered the organ of life. The fact that it reflects the human personality if cold hearted, warm hearted, hard hearted, or stout hearted are well known value judgements.

Transplant surgery signifies other things besides function. Historically, legends of the creation of man tell us something about our attitudes today. As an illustration of such symbolism, one may turn to the *Timaeus* of Plato: "...since one part was better and one worse, and they planted that part of the soul which partakes of courage and spirit, and is a lover of victory, near the head so that it might hearken to reason."

It is of interest to note the role of the heart, which is stated to be "the junction of the veins and the front of the blood which circulates vigorously through

all the limbs—to the end that when the heat of passion boils up, as soon as reason passes the word round that some unjust action is being done which affects them, either from without or possibly even from the interior desires, every organ of sense in the body might quickly perceive through all the channels both the injunctions and the threats, and in all ways obey and follow them, thus allowing their best part to be the leader of them all” (2).

Dr. Samuel Basch, a colleague in the Department of Psychiatry, has been working with the Kidney Transplant Team, and has had some opportunity to study recipients of such transplants, and in some instances the families and donors. Two observations serve to highlight some of the problems:

“A 15-year-old boy had two kidney transplantations, one in 1966, and the second in 1967. The patient discussed his first transplant with great trepidation. He stated it was very disturbing to receive a kidney from a man who had shot himself in the head. The kidney was rejected after 6 months, and the second transplanted kidney was donated by the patient’s 26-year-old brother. The patient referred to his feelings prior to the second procedure as follows: ‘I did not want my brother’s kidney in the first place. In fact, I didn’t want a transplant. I feared my brother’s kidney would go wrong and I would die. The family insisted I have the operation. I did not want to upset everybody so I agreed to have the operation.’ After the transplant, the patient did well for over a year and a half, but one morning he went into a panic in clinic and screamed, ‘Take out this kidney. I don’t want it anymore. You can have your damn kidney. I don’t want any part of it.’ Questioned by a nurse, he stated that his brother, the donor, was a homosexual, and he did not want a homosexual kidney inside of him. He told a doctor he was dissatisfied with the kidney since he had noticed on the chart that his BUN was elevated, and he feared that he would die. At this point he went on a stringent diet and lost 40 pounds. The reason he gave for the diet was that he wanted to be in better shape since he was ‘too soft and round,’ and he wanted to feel and appear stronger. To a psychoanalyst there seems to be a relationship between ‘the homosexual kidney’ and the defense by a more clearly masculine appearance.”

The second patient was a 10-year-old boy, who died. According to the information, he initially refused to accept as a donor his father, who had abandoned the family when the patient was very young, and to whom the patient was extremely hostile. Without the boy’s knowledge, his father’s kidney was transplanted into him. He did well until 6 months later, when his father turned up unexpectedly and revealed the source of the transplanted kidney. This upset the patient, and the next day he was rushed to the hospital moribund, and died with a white blood cell count of 200, explained by the doctors as likely from an overdose of Imuran, the immunosuppressant drug being used. Here, father’s kidney may have represented a bad father who was inside of him.

Kidney donors also manifest certain problems. Dr. Carl Fellner (3) studied 12 donors 5 weeks and 18 months after they sacrificed a kidney. Two were mothers, the rest were a brother and sister. It seems that when the request to

become a donor was made, an immediate decision was arrived at by eight of them, and there was no weighing the alternatives. Four went along with the test, hoping that it would be someone else who would become the donor. None considered refusing, and when it turned out that they were the persons best suited, they committed themselves. All commented that they felt "good," "noble," "bigger," and "happier," and some felt that they had done a great thing for someone else. It is of interest that these were conscious reasons given by the donors, all of which would fit a rather conventionalized attitude in a unique stressful situation.

John Kemph reported that since all "donors developed at least a mild degree of depression following surgery, the psychiatrist provided brief supportive psychotherapy allowing them to express hostility in a variety of ways. Although most of the donors were no longer depressed after 2 weeks, occasionally one was seen in outpatient follow-up for either depression or some other emotional disturbance that existed prior to surgery" (4).

There is one other area that I would like to discuss—the question of dialysis in patients with, for the most part, irreparable kidney disease. There is a report from Israel by Kaplan De-Nour and his colleagues on nine patients in chronic hemodialysis who were intensively studied over a 1 year period.

The hypothesis was advanced that the main problem, stress and threat, was the reaction to the dependency on the machines and the staff, and the aggression resulting from this dependency. Some evidence supporting this hypothesis was presented, and it was suggested that evaluation of acceptance of dependency and of aggression might serve as psychological criteria for selection of patients for chronic hemodialysis, home dialysis, or transplantation, as well as a guide for their management.

Some of the clinical manifestations could also suggest brain dysfunction. Psychological tests and EEG study furnished additional proof. Further study, to elucidate the comparative influence of the various factors (psychological and organic), is now being carried on (5).

Psychological and emotional problems were not confined to the patients. Physicians and all members of the teams involved were confronted with major decisions. In many instances it was a decision relating to life and death. In dialysis more machines mean more lives saved, but more machines mean more money spent, and for purely economic reasons many people cannot be treated. Various techniques have been evolved relating to who shall be chosen for treatment.

It seems to be universally agreed that medicine has made tremendous progress in all areas. Certainly this applies to the fields of prevention, diagnosis, and treatment, based on what might be considered some fantastic contributions from the basic and clinical sciences. This somewhat narcissistic evaluation of ourselves is by and large true. It should be noted, of course, that each generation has made a somewhat similar claim, since knowledge has increased with the progression of time. Perhaps the main difference today may be the extensive self-examination relating to these advances. For the purposes

of this brief discussion, it is taken for granted that many of the complex technical problems will be solved with further research and advances in clinical techniques. The problems that are of interest, not only to psychiatry, but to the whole field of medicine, and those disciplines that deal with the human condition are still present, and always will be.

References

1. Martin, D. C., Arnold, J. D., Zimmerman, T. F., and Richart, R. H.: Human Subjects in Clinical Research: A Report of Three Studies, *New Eng J Med* 279:1426-1431, 1968.
2. Kaufman, M. R.: The Greeks Had Some Words For It, *Psychiat Quart* 40:1-33, 1966.
3. Fellner, C., and Marshall, J. R.: Twelve Kidney Donors, *JAMA* 206:2703-2707, 1968.
4. Kempf, J.: The Role of Psychiatrist on Kidney Transplant Team, *Psychosom Med*, 1966.
5. De-Nour, A. K., Shaltiel, J., and Czaezkes, J. W.: Emotional Reactions of Patients on Chronic Hemodialysis, *Psychosom Med* 30:521-533, 1968.

Received for publication March 31, 1969

A Short-Term Evaluation of L-Dopa Therapy in 34 Patients with Parkinsonism

R. J. MONES, M.D., AND T. S. ELIZAN, M.D.

Introduction

L-dihydroxyphenylalanine, or L-Dopa, has been used in the treatment of Parkinsonism since 1961. Although several observers (1-5) had recognized a beneficial effect of L-Dopa when given intravenously, it was Cotzias, Van Woert, and Schiffer (6), in 1967, who first clearly demonstrated that this drug can effectively reverse most of the dysfunction of Parkinsonism, and that it can be given over a long period of time at an exceedingly high oral dosage, if levels are slowly increased. This contribution has not only introduced a practical, effective therapeutic method in Parkinsonism, but has also opened up possibilities in the biochemical treatment of so-called degenerative and chronic neurologic disorders. Since Cotzias' initial results with oral L-Dopa, he and other investigators have confirmed his conclusion (7, 8) that this is a major advance in the treatment of Parkinsonism.

This paper is a report on the first 34 cases treated at The Mount Sinai Hospital with oral L-Dopa. It evaluates the effect of the drug during the hospitalization period of 3 to 5 weeks.

Material and Methods

The first 34 patients with a diagnosis of Parkinsonism who were hospitalized at The Mount Sinai Hospital in New York City, for a trial of L-Dopa (supplied by the Nutritional Biochemical Corporation, Cleveland, Ohio) from November 1, 1968 to March 29, 1969 inclusive, form the study material. This unselected random group of patients represents all types of Parkinsonism of varying age at onset, severity, and etiology. Complete medical and neurologic examinations and the following laboratory investigations were done for baseline data before L-Dopa therapy: EEG; EKG; chest and skull x-rays; CBC and platelets; ESR; urinalysis; L E preparations; Coombes test; PBI; and 12-channel blood tests, which include Ca, P, K, Na, BUN, CO₂, FBS, alkaline phosphatase, SGOT, LDH, bilirubin, uric acid, and A/G ratios. Cerebrospinal fluid for catecholamine studies was collected in some patients. Movies of patients' neurological status (with emphasis on gross motor dysfunction), and special testing by the Occupational Therapy Section of the Department of Rehabilitation were done before treatment. Blood pressures were taken in the supine, and then erect positions, four times daily, before and during L-Dopa therapy. Drugs that were being taken by patients on admission were withdrawn, except for such medication as Digoxin, chloral hydrate, Librium®, Artane®, or belladonna derivatives. The L-Dopa regimen was started with low doses of 250

From the Department of Neurology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

mg per day (250 mg capsule form), and gradually increased by approximately 250 to 500 mg per day, until an optimum dose was reached which conferred maximum neurological improvement with tolerable side effects. This dose reached 6 grams daily in some patients. During the drug trial, patients were examined once or twice daily. Weekly formal neurological examinations were done. Every Monday and Thursday, CBC, platelets, and urines were examined, and every Monday, an EKG and 12-channel blood work were done. Just before hospital discharge, each patient had a repeat EEG, movie, and occupational therapy testing.

Evaluation of a patient's response to L-Dopa therapy was based on serial neurological examinations, movies before and after the drug, and serial occupational therapy testing.

1. Neurological Examinations. The following categories were specifically evaluated:

- A. *Mental status:* any organic mental syndrome.
- B. *Posture.*
- C. *Gait.*
- D. *Rigidity.*
- E. *Akinesia.*
- F. *Tremor.*
- G. *Fine movements.*
- H. *Face and speech abnormalities.*

These categories were grossly rated, once a week, on a 0-4 scale:

- 0 = Normal or no deficit.
- 1 = Mild abnormality.
- 2 = Moderate abnormality.
- 3 = Severe abnormality.
- 4 = Extreme (or maximum) abnormality.

2. Movies. The pre-L-Dopa movie was spliced to the post-L-Dopa movie, and compared on the basis of similar categories and ratings as above.

3. Occupational Testing. This consisted of seven short performance tests, which were timed in seconds:

- A. *Put five blocks in a box.*
- B. *Put five pegs in a peg-board.*
- C. *String ten beads on a needle.*
- D. *Get up from a chair.*
- E. *Walk a set distance of approximately 15 feet.*
- F. *Handwriting samples.*

After reviewing the comparative data from the above studies, an overall rating of each patient was made on a gross scale as follows:

- 1) No improvement.
- 2) Mild improvement: some definite change was noted in performance but patients' general ability to function in society was not necessarily changed.
- 3) Moderate improvement: significant change, so that patient

could live a different type of life, e.g., if he was previously bed-ridden, he could now walk; if she was previously unable to do housework, she could now at least partially care for the house.

4) Marked improvement: excellent or dramatic change in life style of patient.

These patients have all been discharged from the hospital on 3-6 grams of L-Dopa per day. Follow-up has been possible on all of them.

Results

Table I summarizes the response of the 34 Parkinsonian patients treated with L-Dopa during 3 to 5 weeks' hospitalization. Only 3 patients (9%) showed no improvement with the drug. Forty-seven percent had mild improvement, and 44% had moderate to excellent response.

The patient's age at the time of therapy did not seem to influence the degree of response to the drug. Table II shows that varying degrees of response are possible in all age groups.

TABLE I
*Response of 34 Parkinsonian Patients Treated with L-Dopa during
3-5 Weeks' Hospitalization*

No. of Patients (Percentage)	Degree of Improvement
3 (9%)	None
16 (47%)	Mild
9 (26%)	Moderate
6 (18%)	Marked

TABLE II
*Patients' Age at the Time of Treatment, and Response
to L-Dopa*

Age	No. of Patients	Degree of Improvement
40's	2	1 Mild 1 Excellent
50's	5	1 Mild 2 Moderate 2 Excellent
60's	23	1 None 13 Mild 6 Moderate 3 Excellent
70's	4	2 None 1 Mild 1 Moderate

TABLE III
Severity of Disease and Response to L-Dopa

Severity of Disease	No. of Patients	Degree of Improvement
Minimal	3	2 Mild 1 Moderate
Definite	9	1 None 4 Mild 3 Moderate 1 Excellent
Work disability	9	4 Mild 4 Moderate 1 Excellent
Severe	10	2 None 3 Mild 1 Moderate 4 Excellent
End stage disease	3	3 Mild

TABLE IV
Etiological Categories of 34 Parkinsonian Patients

Etiological Categories	No. of Patients	Improvement
Postencephalitic	3	1 Mild 1 Moderate 1 Excellent
Idiopathic	31	
Toxins-Drugs	0	

The severity of the disease at the onset of therapy is analyzed in Table III. Definition of functional categories is as follows:

1. **Minimal:** minor signs without disability.
2. **Definite:** obvious signs and symptoms, but no functional disability.
3. **Work Disability:** inability to do usual work (housework, office work, driving).
4. **Severe:** inability to do normal living activities without help (dressing, eating, shaving).
5. **End-Stage Disease:** confinement to wheelchair or bed, necessitating complete nursing care.

Improvement in varying degrees occurred in all functional categories of the disease, including the most advanced stage.

Table IV gives the clinical etiological classification of the 34 cases. Three

TABLE V

Signs of Parkinsonism in 34 Patients that Significantly Improved during Hospital Stay

Signs of Parkinsonism	Signs Present	Signs Improved	No Improvement
Mental status	11	4	7
Posture	34	16	18
Gait	32	19	13
Rigidity	32	15	17
Akinesia	34	15	19
Tremor	30	15	15
Defective fine movements	34	16	18
Face and speech abnormalities	32	15	17

TABLE VI

Duration of Parkinsonism and Response to L-Dopa

Duration of Disease	No. of Patients	Degree of Improvement	No. of Patients
Less than 2 years	2	Mild	2
2-5 years	13	None	1
		Mild	6
		Moderate	4
		Excellent	2
5-10 years	9	Mild	4
		Moderate	4
		Excellent	1
Over 10 years	10	None	2
		Mild	4
		Moderate	1
		Excellent	3

patients had a definite history of a preceding encephalitis; all three responded to L-Dopa (mild to excellent response). The remaining 31 cases had no specific or readily identifiable etiology; their response to the drug was similar in pattern to that of the postencephalitic cases.

Table V summarizes the signs of Parkinsonism in 34 patients that significantly improved during hospitalization. Eleven patients (about 30%) had varying degrees of organic mental syndrome on admission. Four of these (almost $\frac{1}{3}$) showed significant improvement in mental status with L-Dopa. In general, facial masking and the soft, slurred speech improved first, with later improvement in rigidity, akinesia, posture, and gait. Tremor seemed to improve later in the course of therapy.

Table VI shows that the duration of Parkinsonism at the time of L-Dopa therapy does not appear to be a significant factor in the response to the drug. Improvement occurred in all categories, including disease of over ten years duration.

TABLE VII
*Complications of L-Dopa Therapy during Short-Term Hospitalization
 of 34 Parkinsonian Patients*

Drug Complications	No. of Patients
1. Chorea and other involuntary movements.....	4
2. Cardiovascular:	
hypotension, dizziness.....	9
myocardial infarct.....	1
fibrillation flutter.....	1
3. Transient elevation:	
alkaline phosphatase.....	1
BUN.....	3
4. Nausea.....	9
5. Widened palpebral fissure, lid retraction, and lid lag.....	10
6. Mental changes:	
agitation, paranoia, and delusions.....	6
psychosis.....	1

COMPLICATIONS OF THE DRUG

The primary uncertainty in the therapeutic dose of L-Dopa is in its short-term and long-term toxicity. The drug has been used in high oral doses for only 2½ years by one group of investigators (8). Table VII lists the drug complications we have encountered in these 34 patients during their short-term hospitalization.

1. **Chorea and Other Involuntary Movements.** These occurred in four hospitalized patients, and consisted of irregular, involuntary movements of the mouth, face, and shoulders. These phenomena were dose-related and disappeared when drug dosage was reduced. The incidence of choreiform movements seemed to increase with time, and several of the patients in this group developed chorea on the same dosage of L-Dopa, 2-3 months after hospital discharge. Long-term follow-up studies are obviously needed to determine the real incidence of this phenomena.

2. Cardiovascular:

A. *Hypotension.* Most patients with Parkinsonism have low blood pressure, although rarely, hypertension and Parkinsonism may be present in an occasional patient. In many patients studied in this series, the diastolic and systolic blood pressure diminished 20 mg Hg during L-Dopa therapy. In nine cases the blood pressure drops were greater than 20 mg Hg in diastolic value, and occasional dizziness and faint feelings occurred. Ephedrine, 25 mg tid, has been of limited value in counteracting the hypotensive effect of L-Dopa.

B. One patient in this series sustained a *myocardial infarct* in the hospital. This was a 68-year-old man who had had bilateral thalamotomies in the past. He was a severe Parkinson patient with serious speech, swallowing, gait, and mental changes. During his initial hospitalization, before L-Dopa ther-

apy, he developed an aspiration pneumonia. After recovering from this problem, L-Dopa was started and gradually raised to a level of 3 grams/day. No improvement in his neurologic status was noted. The blood pressure taken four times daily did not show any significant changes from initial values of 110/80. On the 21st hospital day, the patient was noted to have EKG changes suggestive of a myocardial infarct, and the L-Dopa was stopped. The patient developed pneumonitis on the 23rd hospital day, and eventually died on the 37th hospital day of pneumonia and myocardial infarction. No postmortem examination was obtained. This patient's demise may or may not have been related to the L-Dopa therapy. No evidence of a hypotensive effect of the L-Dopa was established in this case.

A second patient (female, aged 68) was treated in the hospital for 6 weeks with L-Dopa. The blood pressures were in the hypotensive range (90/60) before L-Dopa, and did not change greatly during therapy. Attempts at raising her blood pressure with Ephedrine, fluorocortisone, and ace bandages all failed. The patient had a good neurological response to L-Dopa therapy, and was discharged. Six weeks after discharge, she sustained a myocardial infarct. The patient recovered from her cardiac problem, but L-Dopa has not been reinstituted.

C. *Cardiac arrhythmia* was seen in eight patients. In seven of these cases there was evidence of previous arrhythmia. In one case, two episodes of *fibrillation flutter* were documented, whereas on admission only intermittent auricular premature contractions were noted. There was no definite proof in these cases of any adverse effect of the L-Dopa on the cardiac rhythm.

3. **Transient Elevation of Alkaline Phosphatase and BUN.** Transient elevation of alkaline phosphatase was noted in one case, and transient elevation of BUN in three cases.

4. **Nausea.** At least half the patients taking L-Dopa develop slight nausea or anorexia. In many patients this phenomenon disappears, and they appear to tolerate the drug without further G I symptoms. In nine cases the nausea persisted, so the amount of Dopa prescribed was limited to less than 4 grams/day. Ingestion of the Dopa five times daily after meals, with milk, appears to be of some help in alleviating the nausea.

5. **Enlargement of the Palpebral Fissure, Lid Retraction, and Lid Lag.** These had been noted in ten patients. These phenomena usually herald improvement in the Parkinson syndrome, and have not been a cause for reducing or stopping the drug.

6. **Mental Changes.** Agitation, paranoia, and delusions have been noted in four patients, all of whom had previous history of such complaints before L-Dopa therapy. Two other patients who had postencephalitic Parkinsonism, and who did *not* have previous history of mental disturbances, had a transient episode of agitation which cleared within 24 hours of reducing the medication. One patient, with a history of depression, anxiety, and electroshock treatment had a psychotic episode while on L-Dopa. This episode lasted approximately 96 hours, and cleared upon withdrawal of the drug.

7. **Ketone Bodies in Urine.** Routine urine specimens have almost uniformly shown a positive test for ketone bodies during L-Dopa therapy. Although not

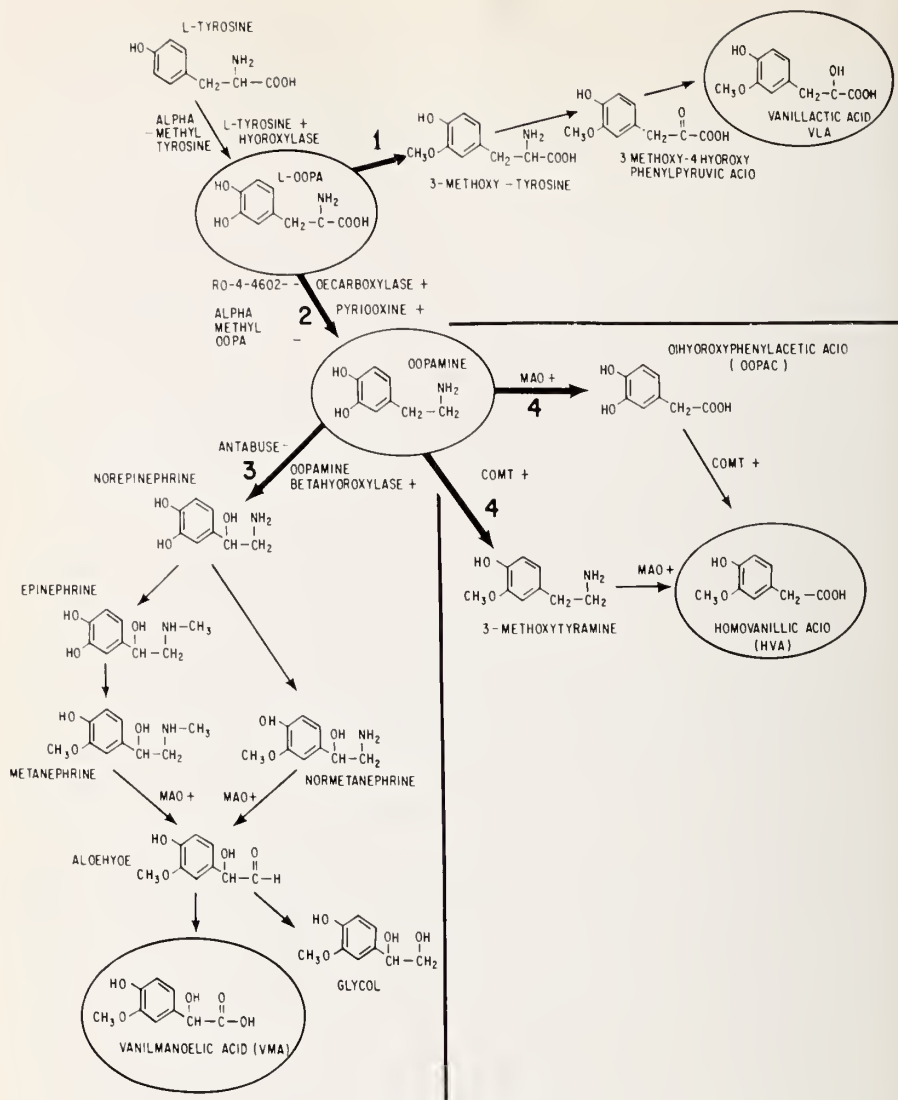


FIG. 1. The three main metabolic pathways of L-Dopa are shown. The major end products found in the urine for each pathway are: Line 1—Vanillic Acid (VLA); Line 3—Vanilmandelic Acid (VMA); and Line 4—Homovanillic Acid (HVA). Most of oral L-Dopa appears to be metabolized along Line 4, as large amounts of Homovanillic Acid are found in the urine of patients receiving L-Dopa. No significant increase in Vanilmandelic Acid or other beta-hydroxylated catecholamines have been found (9). Small amounts of Vanillic Acid (Line 1) appear in the urine. This substance may be the cause of positive tests for ketone bodies in the urine, seen in most patients on high oral doses of L-Dopa.

firmly established, this is probably a false positive test, and indicates the presence of L-Dopa metabolites in the urine (9) (Fig. 1).

SUMMARY OF COMPLICATIONS

The complications of L-Dopa therapy on a *short* term basis have been described. The major area of concern in the short term use of the drug is cardio-

vascular. Any potentially hypotensive drug in elderly patients has some risk. Therefore, any patient with severe vascular disease of the heart, brain, or kidney should not be treated with L-Dopa at this time, unless the Parkinsonism is life-threatening.

Discussion

The historical background of the use of L-Dopa in Parkinsonism is a fascinating story, which starts with the introduction of the drug reserpine in the early 1950's into Western medicine. Reserpine was helpful in decreasing anxiety and blood pressure, but was soon found to cause a Parkinson-like picture after long-term therapy. This toxic state was reversible when reserpine was withdrawn.

The biochemical investigation of this drug led Shore et al (10) to find an increase in urinary serotonin after reserpine therapy. The same year (1957) Carlsson (11) noted that other amines (dopamine) increased in the urine after reserpine therapy, and that the concentration of serotonin and dopamine in the striatum decreased after reserpine therapy. Later, Carlsson (12, 13) noted that Dopa given intravenously reversed many of the effects of reserpine on brain function, whereas 5-hydroxytryptophan did not reverse such effects. The stage was therefore set for further investigation of the role of dopamine in Parkinsonism.

In 1959, Bertler and Rosengren (14) reported on the concentration of serotonin, norepinephrine, and dopamine in the normal human brain. The dopamine had its greatest concentration in the basal ganglia, with almost no dopamine in other parts of the central nervous system. Ehringer and Hornykiewicz (15) confirmed these findings in 1960, and also found the information that the basal ganglia of Parkinson patients have abnormally low concentrations of dopamine, when compared to normal brains. In one case of hemiparkinsonism, Barolin, Bernheimer, and Hornykiewicz (16) noted that the putamen and caudate nuclei contralateral to the affected limbs had lower concentrations of dopamine than the corresponding ipsilateral nuclei.

Attempts were made during the next 5 years to use this information in the treatment of Parkinsonism. Many observers reported transient improvement in akinesia and rigidity with intravenous L-Dopa therapy (1-5). Oral DL-Dopa was administered to patients in dosages up to 2 grams daily by other workers (17, 18, 19), with little improvement noted. McGeer (20) treated patients with Parkinsonism due to phenothiazine toxicity, and did not find any improvement in the neurological picture with oral doses up to 32 grams of DL-Dopa daily.

Finally, Cotzias et al (6), in 1967, described the first practical method of using the information of the above workers for the treatment of Parkinsonism. High doses of oral DL-Dopa (later L-Dopa) were given in gradually increasing increments, until a dosage range of 4-8 grams/day was reached. Further studies in 1969 by Cotzias (8) and others have confirmed the original results of daily oral L-Dopa therapy in Parkinson patients.

COMMENTS ON VARIOUS PHENOMENA OBSERVED DURING L-DOPA THERAPY OF PATIENTS WITH PARKINSONISM

1. **Hypotension.** The tendency toward low blood pressure in patients with Parkinsonism has never been satisfactorily explained. Other phenomena seen in the disease such as sleep disturbances, oily skin, seborrheic dermatitis, excessive sweating, and increased salivation have been thought to be related to hypothalamic disease, and categorized as "autonomic manifestations" of this disease. The blood pressure changes in Parkinsonism may be another manifestation of hypothalamic involvement. The function of dopamine in the hypothalamus is not known.

The Shy-Drager syndrome (21) (1959) may have some relationship to this general problem. The patient described with this rare syndrome has orthostatic hypotension, lack of sweating, sexual and sphincter disturbances, depression, and a Parkinson-like state with akinesia and rigidity. Dopamine levels have not been determined in these cases, nor is there a report of the response of these patients to L-Dopa.

One of our 34 cases had severe orthostatic hypotension, urinary retention, and Parkinsonism. Although the extrapyramidal syndrome improved with L-Dopa administration, the low blood pressure became a greater problem and eventually limited the amount of L-Dopa administered.

One would have thought that a drug that was the precursor to norepinephrine would have a tendency toward increasing the blood pressure by increasing the amount of norepinephrine in the body. The reverse has been observed, and the lowering of blood pressure and orthostatic hypotension is probably the most serious potential danger in L-Dopa therapy.

Biochemical data have shown that there is no significant elevation in the beta-hydroxylated metabolites of L-Dopa. The bulk of L-Dopa appears to be metabolized to homovanillic acid, as approximately $\frac{1}{3}$ to $\frac{1}{2}$ of the oral L-Dopa can be shown to be eventually excreted in the urine as homovanillic acid (9) (Fig. 1). Therefore, the lowering of the blood pressure with L-Dopa may be due to a flooding of the body with dopamine or other unknown metabolites which block alpha receptors, and therefore reduce the response to the normally available norepinephrine.

An effective method of counteracting the hypotensive action of L-Dopa is not yet available. Ephedrine in doses up to 100 mg has had limited use in decreasing the orthostatic hypotension. Schildkraut et al (22) reported in 1963 that the combination of a monoamine oxidase inhibitor and oral L-Dopa in doses of 200-300 mg will cause an increase in blood pressure for 2-4 hours. In one of our cases in this series, a trial of monoamine oxidase inhibitor and L-Dopa was carried out with unsatisfactory neurological response, although we have confirmed that the two drugs in combination will cause an increase in blood pressure. Further work along this line is warranted.

2. **Dyskinesia (Chorea and Athetosis).** Although only 10% of the hospitalized patients in this series developed chorea, subsequent follow-up of these patients has revealed an increase in incidence (up to 30%) after 4

months of therapy. Although not dangerous, as the phenomenon regresses when the dose of L-Dopa is reduced, the chorea is a problem to some patients, and is frequently a limiting factor in the amount of drug an individual patient can take.

The chorea most commonly involves the facial muscles, lips, neck and, less often, the extremities. Rarely, patients note involuntary clenching of toes, panting and sighing respirations, or swallowing trouble. The sites of these dyskinesias appear to be unrelated to the primary symptomatology, and are remarkably consistent in location in any individual patient. Individual tolerances differ, as patients on 2.5 grams of L-Dopa may have this complication, whereas others on 10 grams may not develop chorea. These abnormal movements will usually regress within 48 hours after reduction of drug dosage.

The cause of these movements is not known. Whether normal patients on L-Dopa will develop similar involuntary movements has not yet been studied. Our experience with L-Dopa given to a few patients with dystonia, Huntington's chorea, and other central nervous system disorders is limited, but we have not yet observed chorea developing in these patients.

Treatment with Benadryl®, Symmetrel®, Sparine®, B₆, and 5-hydroxytryptophan (23) have not been of proven value in eliminating the chorea. Further work is needed in understanding the cause, anatomical location, and treatment of this unusual reaction to L-Dopa.

3. Mental Status. A relatively high incidence of depression in Parkinson patients has been observed, but has never been adequately explained. The fact that reserpine can cause the combination of Parkinsonism and depression, would support the impression that depression is part of the Parkinson syndrome, and not primarily a reaction to a disabling neurologic disease.

L-Dopa has been found by Cotzias et al (6, 8) to cause a mood change and a feeling of well being. Recently, L-Dopa was used as a treatment for primary depression with good results (24). We have not found any definite change in depression attributable to the drug; however, agitation, excitement, and paranoia have been noted. Two patients with postencephalitic Parkinsonism have shown a sensitivity to the drug, with a hypomanic behavior occurring on relatively low doses of L-Dopa.

A single patient had a psychotic reaction in the hospital while on L-Dopa. He recovered with withdrawal of the drug, and has had *no* trouble on restarting the drug to levels of 3 grams/daily.

Although L-Dopa has a definite effect in mood in some patients, it is difficult at this time to determine its exact role on affect and general behavior. Patients with history of psychotic behavior, manic states, or paranoia should be treated with great care.

4. Palpebral Fissure. Approximately 30% of patients receiving 4-5 grams of L-Dopa/day developed a widening of the palpebral fissure, lid lag on downward gaze, lid retraction on forward gaze, and an increase in the "stare" of Parkinsonism. No change in pupillary function or accommodation has been seen, and therefore this is probably a local peripheral effect on the sympa-

thetic system of the upper lid, and not a central effect on the brain stem. A reduction in a dose of L-Dopa eliminates these phenomena.

5. **Gastrointestinal Tract.** Nausea, anorexia, and vomiting can be a serious limitation to the use of oral L-Dopa. The same problem has been described by European workers when L-Dopa was given *intravenously*, and therefore this may be a central effect on the brain and not a local gastrointestinal reaction. Decreasing the rate of absorption of L-Dopa with administration of the drug six times daily after food intake, has helped eliminate this problem in many patients.

6. **Skin.** The cause of the high incidence of seborrheic dermatitis in patients with Parkinsonism is not known. The sebaceous glands are affected by hormones (25), and therefore it is possible that the hypothalamus plays some part in the pathophysiology of the skin manifestations of Parkinsonism. It is not yet clear if L-Dopa has a definite effect on this facet of Parkinsonism.

7. **Heart.** The complete effect of L-Dopa and/or metabolites of L-Dopa on the heart is not known. There is no indication of any adverse effect on the heart muscle, and many patients with a history of congestive heart failure have been treated with L-Dopa with excellent results. Digitalis preparation has been used in conjunction with L-Dopa with no evidence of toxicity.

A large number of our patients in the older age group have cardiac arrhythmias such as ventricular premature contractions, auricular premature contractions, atrial fibrillations, and bigeminy rhythm. As these cardiac arrhythmias are intermittent in some cases, it is difficult to incriminate a drug as the cause of the arrhythmia at a given period of time.

There is no proof in evaluating our cases that L-Dopa was responsible for initiating an arrhythmia. As a precaution, however, quinidine, or digitalis has been given to some of our patients before and during L-Dopa therapy.

Summary and Conclusions

The results and complications of oral L-Dopa therapy on 34 Parkinsonian patients hospitalized for 3 to 5 weeks at The Mount Sinai Hospital in New York City are reported and discussed. This short-term evaluation confirms previous reports that oral L-Dopa is a significant advance in the treatment of Parkinsonism. Approximately half of our patients improved dramatically enough within this short period of observation, so that their style of life was changed significantly. Only about 10% showed no discernible improvement with the drug. Long-range experience with L-Dopa is obviously needed. Many basic questions about the drug remain unanswered. A historical review of the use of L-Dopa in Parkinsonism is briefly summarized.

References

1. Birkmayer, W., and Hornykiewicz, O.: Der Dihydroxyphenylalanine (L-Dopa) Effekt bei der Parkinson-Akinese, *Wien Klin Wschr* 73:787-788, 1961.
2. Birkmayer, W., and Hornykiewicz, O.: Der L-Dioxyphenylalanine Effekt beim Parkinson-Syndrom des Menschen zur Pathogenese und Behandlung der Parkinson-Akinese, *Arch Psychiat Nervenks* 203:560-574, 1961.

3. Gerstenbrand von E., Pateisky, K., and Prosenz, P.: Erfahrungen mit L-Dopa in der Therapy des Parkinsonismus, *Psychiat Neurol (Basel)* 146:246-261, 1963.
4. Birkmayer, W., and Hornykiewicz, O.: Weitere Experimentelle Untersuchungen über L-Dopa beim Parkinson Syndrome und Reserpin-Parkinsonismus, *Arch Psychiat Nervenkr* 206:367-381, 1964.
5. Bruno, A.: Effect of L-Dopa on Pharmacological Parkinsonism, *Acta Psychiat Scand* 42:264, 1966.
6. Cotzias, G. C., Van Woert, M. H., and Schiffer, L. M.: Aromatic Amino Acids and Modification of Parkinsonism, *New Eng J Med* 276:364-369, 1967.
7. Yahr, M. D., Duvoisin, R. C., Iloehn, M. M., Shear, M. J., and Barrett, R. E.: L-Dopa (L-3, 4-Dihydroxyphenylalanine): Its Clinical Effects in Parkinsonism, *Trans Amer Neurol Ass* 93:56-63, 1968.
8. Cotzias, G. C., Papavasiliou, P. S., and Gellene, R.: Modification of Parkinsonism-Chronic Treatment with L-Dopa, *New Eng J Med* 280:337-45, 1969.
9. Naftchi, N. E.: Personal Communication, 1969.
10. Shore, P. A., et al: Role of Brain Serotonin in Reserpine Action, *Ann NY Acad Sci* 66:609, 1967.
11. Carlsson, A., Rosengren, E., Bertler, A., and Nilsson, J.: Effect of Reserpine on the Metabolism of Catecholamines, In *Psychotropic Drugs*, Elsevier Publications Co., Amsterdam 1957, 6:363.
12. Carlsson, A., Lindqvist, M., and Magnusson, T.: 3,4-Dihydroxyphenylalanine and 5-Hydroxytryptophan as Reserpine Antagonists, *Nature (London)* 180:1200, 1957.
13. Carlsson, A., Lindqvist, M., Magnusson, T., and Waldeck, B.: On the Presence of 3-Hydroxytyramine in Tissues and the Occurrence of this Amine in Brain, *Science* 127:471, 1958.
14. Bertler, A., and Rosengren, E.: Occurrence and Distribution of Dopamine in Brain and Other Tissues, *Experientia* 15:10-11, 1959.
15. Ehringer, H., and Hornykiewicz, O.: Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des Extrapyramidalen Systems, *Klin Wschr* 38:1236-1239, 1960.
16. Barolin, G. S., Bernheimer, H., and Hornykiewicz, O.: Seitenverschiedenes Verhalten des Dopamins (3-Hydroxytyramin) in Gehirn eines Falles von Hemiparkinsonismus, *Schweiz Arch Neurol Psychiat* 94:241-248, 1964.
17. Greer, M., and Williams, C. M.: Dopamine Metabolism in Parkinson's Disease, *Neurology* 13:73-76, 1963.
18. Friedhoff, A. J., Hekimian, L., Alpert, M., and Tobach, E.: Dihydroxyphenylalanine in Extrapyramidal Disease, *JAMA* 184:285-286, 1963.
19. McGeer, P. L., and Zeldowicz, L. R.: Administration of Dihydroxyphenylalanine to Parkinsonian Patients, *Canad Med Ass J* 90:463-466, 1964.
20. McGeer, P. L., et al: Drug Induced Extrapyramidal Reactions, Treatment with Diphenylhydramine Hydrochloride and Dihydroxyphenylalanine, *JAMA* 177:665-670, 1961.
21. Shy, G. M., and Drager, G. A.: A Neurologic Syndrome Associated with Orthostatic Hypotension, *Arch Neurol* 2:511-527, 1960.
22. Schildkraut, J. J., et al: Biochemical and Pressor Effects of Oral DL-Dihydroxyphenylalanine in Patients Pretreated with Antidepressant Drugs, *Ann NY Acad Sci* 107:1005-1015, 1963.
23. Cotzias, G.: Personal Communication, 1969.
24. Bunney, W. E., et al: Effect of L-Dopa on Depression, *Lancet* 1:885, 1969.
25. Pochi, P. E., Strauss, J. S., and Mescon, H.: Sebum Production and Fractional 17-Ketosteroid Excretion in Parkinsonism, *J Invest Derm* 38:145-51, 1962.

CLINICO-PATHOLOGICAL CONFERENCE

Anasarca and Coma in a Young Male

Edited by

FRANKLIN M. KLION, M.D.

A 30-year-old male was admitted to the hospital in a comatose state. Five months earlier, he had received tetracycline therapy for pharyngitis. Two weeks later he developed anasarca and was admitted to The Mount Sinai Hospital. Previously he had been in good health, and denied renal or heart disease.

The blood pressure was 120/80, pulse 73/min, and respirations 16/min. The optic fundi were unremarkable, and examination of the heart and lungs was normal. The abdomen was distended and a fluid wave was elicited. There was moderate pitting edema of the lower extremities and scrotum. The neurologic examination was normal. The hemoglobin was 14.6 gm, the erythrocyte sedimentation rate 92 mm/hr, and the white blood cell count 5,300/mm³, with a normal differential count. The urine specific gravity was 1.016. There was marked proteinuria. The urinary sediment contained granular casts, 2-4 red blood cells, and 3-4 white blood cells per high power field. The blood urea nitrogen was 16 mg%, fasting blood sugar 90 mg%, creatinine 1.3 mg%, and cholesterol 397 mg%. An antistreptolysin O titer was 1:16, and L E preparation was negative. The serum albumin was 1.5 gm%, alpha₁ globulin 0.14 gm%, alpha₂ 1.25 gm%, beta 1.60 gm%, and gamma 0.29 gm%. A serologic test for syphilis was positive. An intravenous pyelogram and x-ray examination of the chest were normal. A throat culture grew normal flora.

He was treated with salt and water restriction, and a course of penicillin therapy. During the first week in the hospital, the urinary output ranged between 700-900 cc/24 hr. Subsequently, the urine volume increased to 1-2 liter/24 hr. Prednisone therapy was begun, and 1 month later he was discharged.

At home, he lost weight and the dose of prednisone was tapered to 10 mg/day. He remained relatively well until 1 week prior to readmission, when he noted a sudden increase in weight. Prednisone was increased. On the day of entry he reported a fainting spell to his physician.

On admission, he was comatose and unresponsive to painful stimuli, although there was spontaneous motion of all extremities. The blood pressure was 158/104, pulse 64/min, respirations 26/min, and temperature 98°F. The heart, lungs, and abdomen were normal. There was moderate edema of the lower extremities. The right eye was deviated inferiorly, and did not move with oculocephalic maneuvers. Both pupils were miotic and reacted sluggishly to light. The extremities were flaccid. Neither deep tendon nor pathologic reflexes were elicited. The hemoglobin was 14 gm%, the erythrocyte sedi-

mentation rate 92 mm/hr, and the white blood cell count 6,500/mm³, with a shift to the left. The urine specific gravity was 1.010. There was marked proteinuria, and the sediment contained 2-4 red blood cells, and 5-6 white blood cells per high power field. The blood urea nitrogen was 10 mg%, blood glucose 96 mg%, serum sodium 137 mEq/L, potassium 4.2 mEq/L, chlorides 105 mEq/L, and carbon dioxide 29.5 mEq/L. The serum albumin was 1.0 gm%, alpha₁ globulin 0.36 gm%, alpha₂ 2.1 gm%, beta 1.6 gm%, and gamma 0.53 gm%. The serum cholesterol was 985 mg%.

He remained comatose. Repeat examinations on the day of admission showed changing neurologic signs of brain stem dysfunction. Movements were limited to the right side of the body, and the reflexes were hyperactive bilaterally. A tracheostomy was performed, and corticosteroid therapy continued. The spinal fluid was clear and contained 19 red cells/mm³. The glucose was 74 mg%, and protein 4 mg%. The spinal fluid pressure was 170 mm H₂O. A Wasserman test was nonreactive. Skull and x-ray examinations of the chest were normal. On the second hospital day, a left carotid cerebral angiogram showed a small avascular area in the left parietal region and contralateral filling. The right carotid angiogram failed to visualize vessels above the carotid syphon. The following day his temperature rose to 103°F. Physical examination was unchanged. The white blood cell count was 21,000/mm³, with a shift to the left. Penicillin and streptomycin therapy was instituted. On the fourth day the pupils became dilated. Fundoscopic examination was normal. Despite supportive care the patient remained in deep coma, and expired 2 days later.

*Dr. E. Rubin**: The case for discussion is quite interesting, and Dr. Berger has kindly consented to discuss it for us.

*Dr. L. Berger***: A 30-year-old male developed anasarca following an upper respiratory infection for which he received tetracycline, a drug known to aggravate renal insufficiency and to cause renal tubular acidosis, but not known to cause the nephrotic syndrome. He was normotensive, and BUN, blood sugar, and hemoglobin were normal. Proteinuria, hypoalbuminemia, elevated alpha₂ and beta₁ globulins, a diminution of gamma globulin, and hypercholesteremia, however, are characteristic of the nephrotic syndrome. The positive serologic test for syphilis raises a question of lues; however, the nephrotic syndrome associated with syphilis usually occurs with secondary lues.

He was treated with salt and water restriction, penicillin, and corticosteroids, and improved. Four months later edema recurred, and the dose of prednisone was increased.

Upon admission to the hospital, he was comatose and mildly hypertensive. He was edematous and the biochemical findings of the nephrotic syndrome

* Professor of Pathology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

** Assistant Clinical Professor of Medicine, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

were present, without manifestations of renal insufficiency, diabetes, anemia, or an electrolyte imbalance. Dysfunction of the central nervous system, predominantly the brain stem, dominated the clinical picture, and a carotid angiogram showed occlusion of the right carotid artery and an avascular area in the left parietal area. The spinal fluid was normal except for 19 red blood cells/mm³. A serologic test for syphilis performed on the spinal fluid was non-reactive, and this excludes syphilis as a cause of his illness.

Prior to his death, fever and leukocytosis developed, and the patient died without regaining consciousness. Before I proceed with the differential diagnosis, I would like Dr. Antin to review the carotid angiograms.

*Dr. S. Antin**: The right carotid angiogram visualized the common carotid artery in the neck, and a small portion of the internal carotid artery beyond the bifurcation. Some external branches were seen, but there was no visualization of the intracranial vessels of the right cerebral hemisphere. This is not the picture that is commonly seen with atherosclerotic disease involving the internal carotid artery in the neck, but a precise etiology cannot be ascertained on the basis of the examination.

Dr. Berger: Dr. Antin, does the failure to demonstrate collateral vessels suggest an acute occlusion?

Dr. Antin: Failure to demonstrate collateral circulation only indicates that large vessels are involved. In this case, the occlusion was of the carotid artery in the neck and carotid syphon. The left carotid angiogram, in an early arterial phase, showed the bifurcation of the common carotid artery and its branches. Intracranially, the anterior and posterior cerebral arteries were well visualized. All the major branches of the middle cerebral artery, however, were not seen, and there was a wedge-shaped avascularity area in the region of the parietal lobe. A parietal branch of the middle cerebral artery filled in a retrograde fashion, indicating that there was an occlusion of a middle cerebral artery branch intracranially with collateral circulation. When we combine the right carotid study with the left carotid study, there is evidence for both large vessel and small vessel occlusive disease.

Dr. Berger: Thank you, Dr. Antin.

The first aspect of this patient's illness I wish to consider is the etiology of the nephrotic syndrome. I suspect that the nephrotic syndrome, although preceding the terminal episode, was probably of secondary importance, and was not a manifestation of his primary disease. There are many diseases which are found in association with the nephrotic syndrome. Some of them produce characteristic histology changes in the kidney, such as the proliferative glomerulonephritis of diabetes. When the nephrotic syndrome is found coexistent with other systemic diseases, the histologic picture is not diagnostic in the sense that the foot process or membranous changes found in the glomerular interstitium are nonspecific. I think that this differentiation is important in attempting to determine the etiology of the nephrotic syndrome in this patient.

* Assistant Professor of Neurology and Radiology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029.

We used to think that a patient with the nephrotic syndrome had one of several disease processes which included glomerulonephritis, idiopathic nephrotic syndrome, diabetes mellitus, amyloidosis, vena cava thrombosis, or systemic lupus erythematosus. Shreiner, however, has catalogued many more possible etiologic causes of the nephrotic syndrome. Polyarteritis nodosa; Takayasu's syndrome, which is a disease that I'll mention later; various allergens, such as bee stings and poison ivy; and various nephrotoxins, such as organic and inorganic materials may be associated with the nephrotic syndrome. Also listed are circulatory states, including congestive heart failure, tricuspid insufficiency, constrictive pericarditis, and various familial syndromes; infectious diseases; and a group of miscellaneous causes, the most interesting being pregnancy and transplanted kidneys.

Prior to his terminal episode, none of the usual causes for the nephrotic syndrome (other than the idiopathic variety) were apparent. I can exclude diabetes, amyloidosis, allergens, toxins, and circulatory disorders. The idiopathic nephrotic syndrome is characterized by changes of the basement membrane, or the epithelial foot processes of the glomerulus. Renal function is usually well preserved, except for the altered permeability of glomerulus to protein. The well preserved renal function and the lack of formed elements in the urine, therefore, exclude proliferative or subacute glomerulonephritis, although secondary lues should be considered, especially since the patient had a positive serologic test.

In view of the patient's terminal episode, we have to consider that he had an arteritis which presented itself late in life, and ultimately led to his demise. The patient died of central nervous system disease without previous symptoms. The fainting episode 1 week before may have been due to oligemia secondary to hypoalbuminemia. The arterial vascular occlusion of the central nervous system most likely was part of the primary pathologic process, and raises several possibilities. Multiple congenital vascular abnormalities or multiple thromboses would be unusual, and simultaneous occlusion of several arteries by embolism is rare. More likely, the patient had a disseminated occlusive disease involving the larger arteries. The hypercholesteremia for the 5 months prior to his demise may have resulted in severe arteriosclerosis of his cerebral arteries. However, even if this short period of hypercholesterolemia had been sufficient to produce significant changes in the blood vessels, it would be unusual for the arteriosclerosis to be limited only to the vessels of the brain.

Syphilis should be mentioned again to recall that prior to the introduction of penicillin, arteritis due to syphilis frequently involved the central nervous system.

The nephrotic syndrome may also be a reflection of an "allergic" hyperimmune phenomenon. Deposition of antibody on the basement membrane has been reported in the nephrotic syndrome, and antikidney antiserum can produce a nephrotic syndrome in rats. The L E preparation was negative, and the arteritis in lupus tends to involve small vessels. We need not consider polyarteritis nodosa, because of the absence of involvement of other organs be-

side the kidney. Polyarteritis nodosa also produces a small vessel arteritis. There is another group of arteritides which involve the central nervous system, and can possibly be related to the nephrotic syndrome.

Takayasu's syndrome is an arteritis originally described by a Japanese ophthalmologist. It occurs more frequently in females, and it usually involves the aortic arch, or produces stenosis of blood vessels which emanate from the aortic arch. The clinical signs depend on the specific artery involved. Another distinct clinical syndrome is temporal arteritis, which occurs in the elderly and is usually associated with headache and eye signs. Both are characterized pathologically by granuloma formation with giant cells in the inflammatory reaction around the arteries. Wegner's granulomatosis also tends to affect small blood vessels. Feigin and others have described a noninfectious granulomatous arteritis occurring in people in their middle years which, although rare, is associated with granulomatous formation.

Thromboangiitis obliterans should also be mentioned. Although isolated involvement of vessels of the central nervous system has been reported, it is extremely rare, and may be dismissed.

Having considered possible granulomatous diseases, I should also mention sarcoidosis. Granulomas occur in the parenchymatous tissue, but if they impinge on blood vessels, they may cause vascular occlusion. This diagnosis would be unlikely in the absence of other manifestations of sarcoidosis. I find it most tempting, therefore, to consider that this patient had an arteritis, probably granulomatous in nature, involving the large cerebral arteries. The nephrotic syndrome, histologically, should show changes of the basement membrane, rather than solely foot process changes.

Dr. Rubin: Thank you, Dr. Berger. Are there any questions?

Speaker from the Floor: Is there an increased incidence of atherosclerosis in patients with the nephrotic syndrome of long standing?

Dr. Berger: My own observations and the literature do not support this.

Dr. Rubin: Sometimes, as illustrated by the present case, the pathologist cannot clearly define the pathophysiologic process, but can only present the morphologic findings and attempt to correlate them with the clinical picture.

The kidneys were of normal size. The right kidney weighed 140 grams, and the left 150 grams. The main renal arteries and aorta were free of significant atherosclerosis, and the glomeruli and the renal tubules were microscopically normal (Figs. 1 and 2). The afferent arterioles also appeared to be entirely normal. In the nephrotic syndrome, namely those cases unassociated with light microscopic changes, the glomeruli have been described as appearing too perfect. It may be that the basement membranes of such glomeruli are rigid and that this accounts for their excellent staining properties.

A renal biopsy was performed prior to death, which was not mentioned in the clinical protocol. The histologic appearance was typical of idiopathic lipoid nephrosis, with many tubular cells filled with fat. There are two distinctive types of pathologic changes seen in the nephrotic syndrome. A silver stain of the kidney in one type shows small projections or spikes extending from the base-

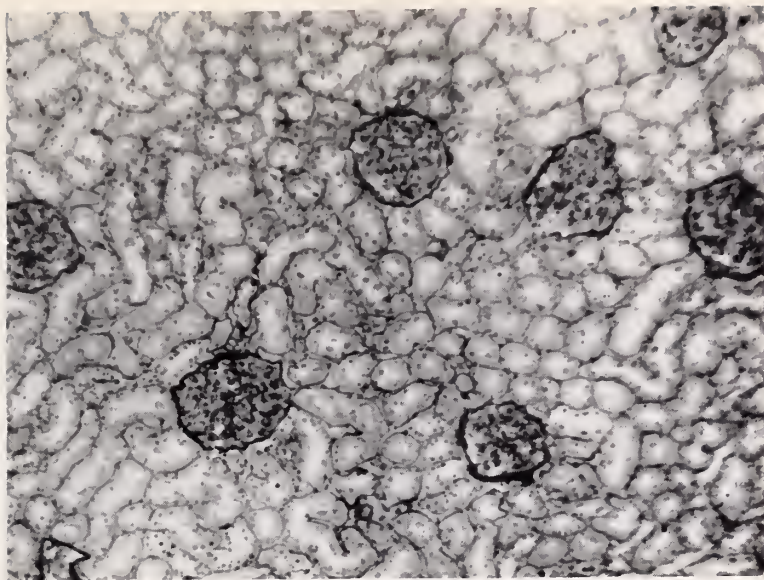


FIG. 1. Section of kidney showing normal architecture (PAS $\times 40$).

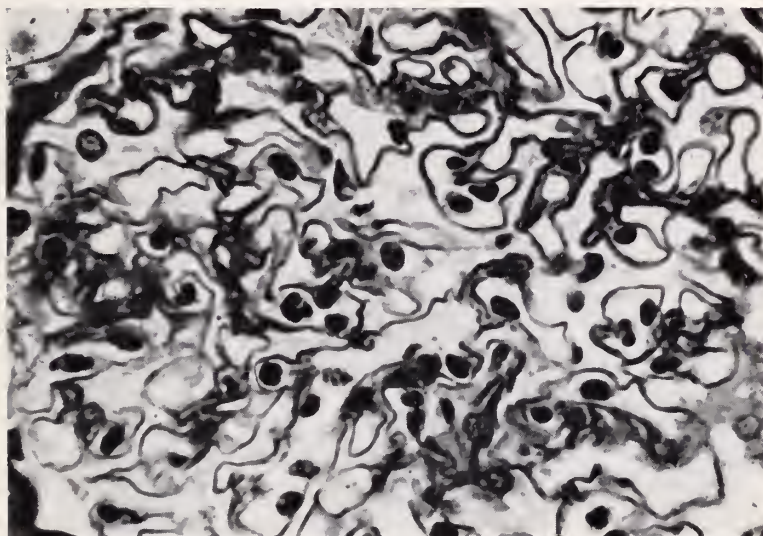


FIG. 2. High power micrograph of kidney showing normal basement membrane (PAS $\times 400$).

ment membranes, which appear nodular. When a section of kidney of this patient was examined with a silver stain, the basement membranes were smooth, without beading.

When the kidney of the first type of case is examined with the electron microscope, the basement membrane appears thickened, and there are nu-

merous amorphous deposits within the basement membrane. In addition, the foot processes are enlarged. This particular type of membranous change in the glomerulus probably accounts for the nephrotic syndrome. Presumably, the basement membrane acts as a filter. When it is diseased, it allows free movement of protein.

In the case which we presented today, the basement membrane was smooth and indistinguishable from normal, electron microscopically. The foot processes of the epithelial cells which are normally applied to the basement membrane, however, were distorted. This, then, not only represents a membranous disease of the glomerulus, but also a disease of the foot processes. Pathophysiology, however, is more complex.

Using the fluorescein tagged antigamma globulin antibody technique, kidney sections from the first type show thickening and beading of the basement membrane, corresponding to the deposits seen with the electron microscope, and to the projections visible in the silver stain. These deposits are presumably antigen-antibody complexes which become trapped in the basement membrane. These antibodies are not necessarily directed against the basement membrane of the kidney, and may be nonspecific.

In the case under discussion, a different pattern was seen. The gamma globulin was found throughout the basement membrane, in a beaded fashion, but uniformly (Fig. 3). This distribution of gamma globulin probably indicates the presence of an antibody directed against the basement membrane.

Occlusive vascular disease was found in many organs. In a large vessel of the prostate, there was an organized thrombus without an inflammatory reaction or evidence of an arteritis. Agglutinated platelets were seen in a recent thrombus in a pancreatic vessel, and an organized thrombus was also present in a large pulmonary artery (Fig. 4). Thrombi were also found in the vessels of the heart. The left ventricle was hypertrophic, perhaps a reflection of his

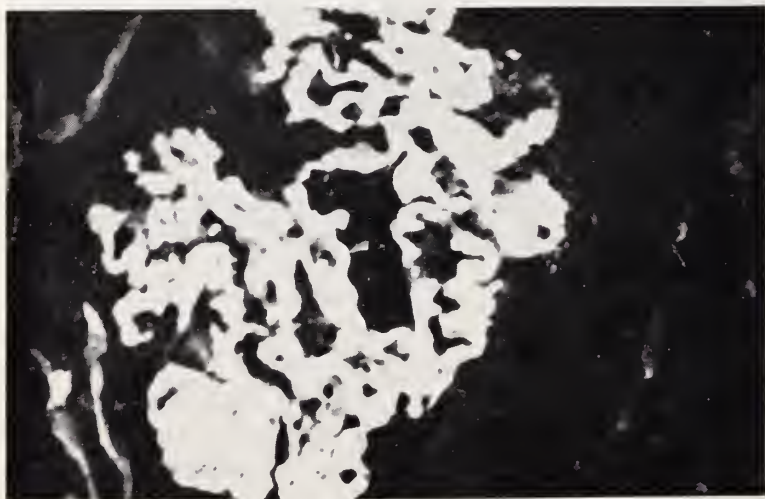


Fig. 3. Section of kidney stained with fluorescein labeled human gamma globulin, showing deposition of immunoglobulins along the basement membrane ($\times 250$).

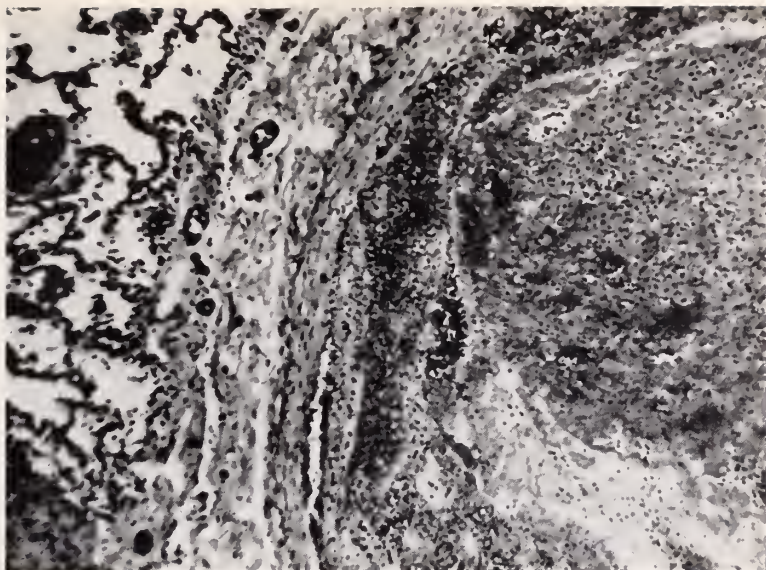


FIG. 4. Thrombus in large pulmonary artery (H & E $\times 200$).



FIG. 5. Embolus in left main renal artery.

moderate hypertension, and there was an area of fibrosis and a mural thrombus in the posterior aspect of the left ventricle. We also found a mural thrombus in the right atrium, and presume that the emboli in the pulmonary vessels originated from it.

There was an embolus in one of the branches of the main renal artery of the left kidney, which probably also originated from the mural thrombus in the left heart (Fig. 5). Numerous areas of infarction were found in the kidney parenchyma (Fig. 6).

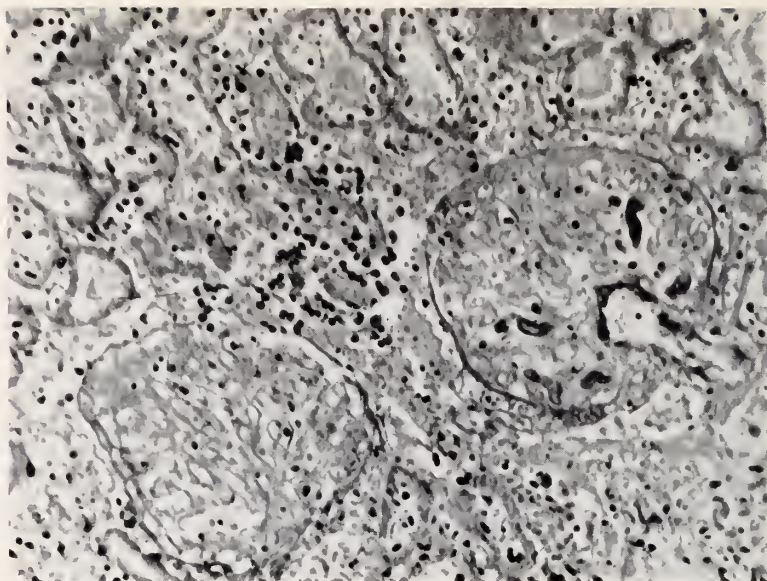


FIG. 6. Area of infarction in renal parenchyma (H & E $\times 200$).



FIG. 7. Area of infarction within the brain, with hemorrhage (H & E $\times 100$).

In the brain, we found a large, recent embolus in the right internal carotid artery, which apparently also originated from the mural thrombus. The right internal carotid was thrombosed, and the right side of the brain was congested and soft (Fig. 7). In many organs of the body, therefore, there were thrombi and emboli in small and large vessels, and no evidence of an arteritis.

I cannot explain all the findings in this case, but would like to comment on two features. Whether the kidney disease was primarily foot process disease, or whether the basement membrane changes were more important, the disorder resulted in severe loss of protein and hypoalbuminemia.

The hyperlipidemia might possibly lead to a hypercoagulability state. There is good evidence to indicate that in conditions such as pancreatic carcinoma, atherosclerosis, pregnancy, the postpartum state, myocardial infarction, and crush injuries, a state of hypercoagulability may exist. Experimentally, high fat diets lead to increase in clotting factors, decrease in fibrinolytic activity of the plasma, and an increased incidence of thrombosis.

Experimentally, fat emulsions given intravenously produce similar results, and also produce intravascular clotting. The intravenous administration of long chain saturated fatty acids also results in massive thrombosis and increased clotting *in vitro*. In addition, there is experimental evidence that plasma lipids produce changes in the vessel wall, possibly by increasing the so-called stickiness.

In summary, this patient had idiopathic lipoid nephrosis. This led to proteinuria, hypoalbuminemia, hyperlipemia, and possibly to hypercoagulability, intravascular thrombosis, and embolism. His basic disease was the nephrotic syndrome; the mural thrombosis and intravascular clotting were probably secondary factors.

Final Diagnoses:

IDIOPATHIC LIPOID NEPHROSIS.

MULTIPLE VASCULAR OCCLUSIONS, INVOLVING KIDNEY, LUNG, AND BRAIN.

References

- Schreiner, G. E.: Nephrotic Syndrome, In *Diseases of the Liver*, Straus, M. B., and Welt, L. G., eds. Little Brown and Co., New York 1963, pp 335-444.
Craviota, H., and Feigin, I.: Noninfectious Granulomatous Angiitis with a Predilection for the Nervous System, *Neurology (Minneapolis)* 9:599-609, 1959.

Received for publication August 8, 1969

INDEX TO VOLUME THIRTY-SIX

- ABNORMAL** axis of labor forces due to laxity of the abdominal wall. (Radiological Notes), 155
- Abt, A. B., and Deppisch, L. M. Multiple myeloma involving the extrahepatic biliary system, 48
- Acidosis, metabolic. (P. Goldfinger), 113
- Acute appendicitis presenting as multiple, extra-abdominal abscesses. (S. A. Geller), 308
- Afterloading multiple irradiators for the treatment of cancer of the corpus of the uterus: A preliminary report of a new device. (N. Simon), 443
- Alexander, S., et al. Peripelvic urine granuloma: Case report, 30
- Alkalosis
diuretic induced. (P. Goldfinger), 117
metabolic. (P. Goldfinger), 117
- Alpert, J. N., and Mones, R. Neurologic manifestations of neuroblastoma, 37
- Amnioscopy. (S. G. Clayton), 454
- Amyloidosis. (T. Kahn, et al), 15
- Anasarca and coma in young male. (Clinico-Pathological Conference), 516
- Anemia, azotemia, and rectal bleeding in a middle-aged female. (Clinico-Pathological Conference), 415
- Aneurysm. (S. S. Schneierson and E. Bottone), 10
- Antibiotic induced apnea. (R. A. Levine, et al), 380
- Aortic
aneurysm infected with *Klebsiella pneumoniae*, Serotype 1: Case report. (S. S. Schneierson and E. Bottone), 10
valve. (P. Marchand), 200
- Appendicitis. (S. A. Geller), 308
- Arkin, Alvin. Obituary, 1
- Arrhythmia. (P. Samet and J. W. Lister), 248
- Ascites, pancreatic. (R. B. Wagner and S. H. Tolins), 216
- Atrioventricular block. (P. Samet and J. W. Lister), 248
- Azotemia, proteinuria, peripheral vascular disease, and fibrothorax in a male with mild diabetes mellitus. (Clinico-Pathological Conference), 55
- BEADLE**, G. W. Medicine in a changing world, 171
- Beck, A. R., Editor, see Unusual Problems in Surgery
- Beiber, M. P., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380
- Benign nodular lymphoid hyperplasia of the small bowel. (Radiological Notes), 430
- Biliary tract. (A. B. Apt and L. M. Depisch), 48
- Biology, molecular. (Francis H. C. Crick), 178
- Bloch, C., Editor, see Radiological Notes
- Bloom, S. M. Cancer of the nasopharynx: A study of ninety cases, 277
- Bluestone, L., and Ramirez-Irizarry, A. A. Carpal tunnel compression syndrome: Unusual case reports, 210
- Bookman, J. J., et al. Tolbutamide in pregnancy and diabetes, 471
- Bottone, S., and Schneierson, S. S. Aortic aneurysm infected with *Klebsiella pneumoniae*, Serotype 1: Case report, 10
- Bradycardia. (P. Samet and J. W. Lister), 248
- Bundle branch block, right. (S. Richmond and L. Pordy), 96
- Burrows, L., Editor, see Unusual Problems in Surgery
- CACATIAN**, J. C., and Kannerstein, M. Hemangioma as a cause of cryptogenic gastrointestinal hemorrhage, 299
- Calcium chloride reversal of polymyxin B-induced apnea. (R. A. Levine, et al), 380
- Cancer of the nasopharynx: A study of ninety cases. (S. M. Bloom), 277
- Cardiac
arrhythmias due to hypersensitivity. (J. Harkavy), 485
pacing. (P. Samet and J. W. Lister), 248
standstill. (P. Samet and J. W. Lister), 248
transplantation in man: Its therapeutic and other importance. (D. A. Cooley), 475
- Carpal tunnel compression syndrome: Unusual case reports. (A. A. Ramirez-Irizarry and L. Bluestone), 210
- Cerebellar glioblastomas. (S. W. Gross, et al), 123
- Chapman, I. The initiating cause of coronary artery thrombosis: An anatomic study, 361
- Churg, J., et al. Nephrotic syndrome in myeloma with amyloidosis, 15
- Chusid, E. L., et al. Severe hypoxemia in an obese patient with polycythemia vera, 21
- Clayton, S. G. The health of the fetus during labour, 454
- Clinico-Pathological Conference, F. M. Klion, Editor
Anasarca and coma in a young male, 516
Anemia, azotemia, and rectal bleeding in a middle-aged female, 415
Azotemia, proteinuria, peripheral vascular disease, and fibrothorax in a male with mild diabetes mellitus, 55
Gastrointestinal bleeding, 236
Polycythemia and transient hypoglycemia in a 77-year-old male, 130
- Cohen, R., et al. Cerebellar glioblastomas, 123
- Colp, Ralph Award, 77
- Congenital disorders. (Sir Peter Medawar), 189

- Cooley, D. A. Cardiac transplantation in man: Its therapeutic and other importance, 475
- Cooper, P., et al. Mesenteric vascular occlusion, 220
- Coronary artery thrombosis, precipitating cause. (I. Chapman), 361
- Corpus. (N. Simon), 443
- Crick, Francis H. C. Molecular biology and medical research, 178
- Current therapy of cystinuria. (H. J. Goldman and S. I. Glickman), 79
- Currents in medical education in the United States. (H. Popper), 348
- Cystinuria. (H. J. Goldman and S. I. Glickman), 79

DANIEL Stats Memorial Prize Winner, 77

- Demonstration of the renal fascia. (Radiological Notes), 158
- Deppisch, L. M., and Abt, A. B. Multiple myeloma involving the extrahepatic biliary system, 48
- Dermoid cyst of the ovary verifying ovarian mobility during pregnancy. (Radiological Notes), 423
- Diabetes
(Sir Peter Medawar), 189
tolbutamide in. (H. Dolger, et al), 471
- Diazepam. (M. A. Nevins, et al), 408
- Digitalis. (M. A. Nevins, et al), 408
- Disorders, congenital. (Sir Peter Medawar), 189
- Disseminated infection by *Mycobacterium fortuitum*. (K. A. Feinberg and S. S. Schneierson), 375
- Distended urinary bladder impeding passage of the fetal head. (Radiological Notes), 156
- Diuretic induced alkalosis. (P. Goldfinger), 117
- Dolger, H., et al. Tolbutamide in pregnancy and diabetes, 471
- Dominguez, C. Daniel Stats Memorial Prize Winner, 77
- Donoso, E., et al. Ineffectiveness of diazepam as an antiarrhythmic agent, 408
- D-penicillamine. (H. J. Goldman and S. I. Glickman), 79
- Dreiling, D. A. Pancreatic disease: A review, 388

ELIZAN, T. S.

- ..., and Mones, R. J. A short-term evaluation of L-Dopa therapy in 34 patients with Parkinsonism, 503
- ..., et al. Experimental teratogenesis in ferrets using rubella virus, 103
- ..., et al. Study of rubella virus as a teratogen in experimental animals: A short review, 108
- Environment, improvement of (Sir Peter Medawar), 189
- Experimental teratogenesis in ferrets using rubella virus. (T. S. Elizan, et al), 103
- Extra-abdominal abscesses. (S. A. Geller), 308

FABIYI, A.

- ..., et al. Experimental teratogenesis in ferrets using rubella virus, 103
- ..., et al. Study of rubella virus as a teratogen in experimental animals: A short review, 108
- Feinberg, K. A., and Schneierson, S. S. Disseminated infection by *Mycobacterium fortuitum*, 375
- Fetal
acid-base balance. (S. G. Clayton), 454
blood sampling. (S. G. Clayton), 454
bradycardia. (S. G. Clayton), 454
head compression. (S. G. Clayton), 454
hypoxia. (S. G. Clayton), 454
tachycardia. (S. G. Clayton), 454
- Forte, F. A., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380
- Friedberg, C. K., et al. Ineffectiveness of diazepam as an antiarrhythmic agent, 408

GALLBLADDER. (A. B. Apt and L. M. Deppisch), 48

- Gastrointestinal
bleeding. (Clinico-Pathological Conference), 236
tract. (J. C. Cacatian and M. Kannerstein), 299
- Geller, S. A. Acute appendicitis presenting as multiple, extra-abdominal abscesses, 308
- Genetics and the medicine of the future. (Sir Peter Medawar), 189
- Gersten, S. P., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380
- Glickman, S. I., and Goldman, H. J. Current therapy of cystinuria, 79
- Glioblastoma. (S. W. Gross, et al), 123
- Goldfinger, P.
Hypokalemia, metabolic acidosis, and hypocalcemic tetany in a patient taking laxatives, 113
Potassium depletion and metabolic alkalosis in a psychiatrically disturbed patient, 117
- Goldman, H. J., and Glickman, S. I. Current therapy of cystinuria, 79
- Goldstein, M. H., et al. Nephrotic syndrome in myeloma with amyloidosis, 15
- Granulocytopenia. (S. B. Levy, et al), 26
- Gross, S. W., et al. Cerebellar glioblastomas, 123

HARKAVY, J. Cardiac arrhythmias due to hypersensitivity, 485

- Health of the fetus during labour. (S. G. Clayton), 454
- Heart block. (P. Samet and J. W. Lister), 248
- Hemangioma as a cause of cryptogenic gastrointestinal hemorrhage. (J. C. Cacatian and M. Kannerstein), 299
- Hematoma of the larynx. (Radiological Notes), 145

- Hemorrhage, cryptogenic. (J. C. Cacatian and M. Kannerstein), 299
- Henoch-Schölein purpura. (Unusual Problems in Surgery), 65
- Hereditary onycho-osteodysplasia. (Radiological Notes), 150
- History, morphologic. (H. Popper), 3
- Homograft valves. (P. Marchand), 200
- Housing, public. (G. W. Beadle), 171
- Hyde Park-Kenwood. (G. W. Beadle), 171
- Hypernephroma with massive perirenal hematoma. (Radiological Notes), 439
- Hypocalcemia. (P. Goldfinger), 113
- Hypokalemia
metabolic acidosis, and hypocalcemic tetany in a patient taking laxatives. (P. Goldfinger), 113
Potassium depletion and metabolic alkalosis in a psychiatrically disturbed patient. (P. Goldfinger), 117
- Hypoxemia. (E. L. Chusid, et al), 21
- I**NEFFECTIVENESS of diazepam as an antiarrhythmic agent. (M. A. Nevins, et al), 408
- Infection, disseminated by *Mycobacterium fortuitum*. (K. A. Feinberg and S. S. Schneierson), 375
- Initiating cause of coronary artery thrombosis: An anatomic study. (I. Chapman), 361
- Irradiators. (N. Simon), 443
- Ischemic colitis: Presentation of seven cases. (Radiological Notes), 324
- K**AHN, T., et al. Nephrotic syndrome in myeloma with amyloidosis, 15
- Kannerstein, M., and Cacatian, J. C. Hemangioma as a cause of cryptogenic gastrointestinal hemorrhage, 299
- Kaufman, M. R. The psychiatrist looks at medical progress, 497
- Klebsiella pneumoniae. (S. S. Schneierson and E. Bottone), 10
- Klion, F. M., Editor, see Clinico-Pathological Conference
- Korenman, G. Neurologic syndromes associated with primary thrombocythemia, 317
- Krugman, M. E., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380
- L**AXATIVE abuse. (P. Goldfinger), 113
- L-Dopa. (R. J. Mones and T. S. Elizan), 503
- Leichtling, J. J., Editor, see Unusual Problems in Surgery
- Levine, R. A., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380
- Levy, S. B., et al. Reversible granulocytopenia in a patient with polycythemia vera taking nitrofurantoin: Report of a case, 26
- Life, mean expectation of. (Sir Peter Medawar), 189
- Lipase. (R. B. Wagner and S. H. Tolins), 216
- Lippmann, Robert K. Obituary, 447
- Lister, J. W., and Samet, P. Selected experiences with cardiac pacing, 248
- M**ANIFESTATIONS, neurologic. (J. N. Alpert and R. Mones), 37
- Marchand, P. The use of valve homografts in cardiac surgery, 200
- Mattes, L. M., et al. Ineffectiveness of diazepam as an antiarrhythmic agent, 408
- Medawar, Sir Peter. Genetics and the medicine of the future, 189
- Medical progress. (M. R. Kaufman), 497
- Medicine
in a changing world. (G. W. Beadle), 171
in a rational society. (L. Pauling), 194
research in. (Francis H. C. Crick), 178
- Mellin, H., et al. Reversible granulocytopenia in a patient with polycythemia vera taking nitrofurantoin: Report of a case, 26
- Mesenteric vascular occlusion. (R. Vijayana-gar, et al), 220
- Metabolic
acidosis. (P. Goldfinger), 113
alkalosis. (P. Goldfinger), 113
- Methotrexate. (S. M. Peck and K. E. Os-serman), 71
- Meyers, B., et al. Reversible granulocytopenia in a patient with polycythemia vera taking nitrofurantoin: Report of a case, 26
- Miller, A., et al. Severe hypoxemia in an obese patient with polycythemia vera, 21
- Mitral valve. (P. Marchand), 200
- Molecular biology and medical research. (Francis H. C. Crick), 178
- Mones, R. J.
..., and Alpert, J. N. Neurologic manifestations of neuroblastoma, 37
..., and Elizan, T. S. A short-term evaluation of L-Dopa therapy in 34 patients with Parkinsonism, 503
- Morphologic history. (H. Popper), 3
- Multiple myeloma involving the extrahepatic biliary system. (A. B. Apt and L. M. Deppisch), 48
- Mycobacterium fortuitum*, disseminated infection by. (K. A. Feinberg and S. S. Schneierson), 375
- Myeloma
multiple. (A. B. Apt and L. M. Deppisch), 48
Nephrotic syndrome in myeloma with amyloidosis. (T. Kahn, et al), 15
- N**AQUI, M. A. Ralph Colp Award Winner, 77
- Nasopharynx, cancer of. (S. M. Bloom), 277
- Natural selection. (Sir Peter Medawar), 189
- Nechemias, C. Tolbutamide in pregnancy and diabetes, 471

- Nephrotic syndrome in myeloma with amyloidosis. (T. Kahn, et al), 15
- Neuroblastoma. (J. N. Alpert and R. Mones), 37
- Neurologic manifestations of neuroblastoma. (J. N. Alpert and R. Mones), 37
- syndromes associated with primary thrombocythemia. (G. Korenman), 317
- Nevins, M. A., et al. Ineffectiveness of diazepam as an antiarrhythmic agent, 408
- Nitrofurantoin. (S. B. Levy, et al), 26
- O**BESITY. (E. L. Chusid, et al), 21
- Obituary
- Arkin, Alvin, 1
- Lippmann, Robert K., 447
- Otani, Sadao, 245
- Rosenthal, Martin C., 345
- Schifrin, Arthur, 451
- Occlusion. (R. Vijayanagar, et al), 220
- Occurrence of type B-Wolff-Parkinson-White conduction in the presence of right bundle branch block. (S. Richmond and L. Pordy), 96
- Organelle pathology. (H. Popper), 3
- Osserman, K. E., and Peck, S. M. Studies in bullous diseases: Treatment of pemphigus vulgaris with methotrexate, two patients (one with concurrent myasthenia gravis), 71
- Otani, Sadao. Obituary, 245
- P**ACEMAKERS. (P. Samet and J. W. Lister), 248
- Pancreatic ascites. Case report: Ascitic fluid lipase utilized for diagnosis. (R. B. Wagner and S. H. Tolins), 216
- disease: A review. (D. A. Dreiling), 388
- Panichavantana, S., et al. Cerebellar glioblastomas, 123
- Parkinsonism. (R. J. Mones and T. S. Elizan), 503
- Pathology, organelle. (H. Popper), 3
- Pauling, L. Medicine in a rational society, 194
- Peck, H. M., Editor, see Radiological Notes
- Peck, S. M., and Osserman, K. E. Studies in bullous diseases: Treatment of pemphigus vulgaris with methotrexate, two patients (one with concurrent myasthenia gravis), 71
- Pemphigus vulgaris. (S. M. Peck and K. E. Osserman), 71
- Peripelvic urine granuloma: Case report (S. Alexander, et al), 30
- Phenylketonuria. (Sir Peter Medawar), 189
- Platelets. (G. Korenman), 317
- Pneumoniae, Klebsiella. (S. S. Schneerson and E. Bottone), 10
- Polycythemia and transient hypoglycemia in a 77-year-old male. (Clinico-Pathological Conference), 130
- Polycythemia vera
- Reversible granulocytopenia in a patient with polycythemia vera taking nitrofurantoin: Report of a case. (S. B. Levy, et al), 26
- Severe hypoxemia in an obese patient with polycythemia vera. (E. L. Chusid, et al), 21
- Polymyxin B-induced apnea. (R. A. Levine, et al.), 380
- respiratory paralysis reversed by intravenous calcium chloride. (R. A. Levine, et al), 380
- Popper, H.
- Currents in medical education in the United States, 348
- The relevance of morphology in medicine, 3
- Pordy, L., and Richmond, S. The occurrence of type B-Wolff-Parkinson-White conduction in the presence of right bundle branch block, 96
- Post-traumatic arteriovenous fistula between carotid artery and ophthalmic vein. (Radiological Notes), 164
- Potassium depletion and metabolic alkalosis in a psychiatrically disturbed patient. (P. Goldfinger), 117
- Pregnancy, tolbutamide in. (H. Dolger, et al), 471
- "Prune-belly" syndrome. (Radiological Notes), 425
- Psychiatrist looks at medical progress. (M. R. Kaufman), 497
- Pulmonary valve. (P. Marchand), 200
- R**ADIOLOGICAL Notes, C. Bloch and H. M. Peck, Co-Editors
- Abnormal axis of labor forces due to laxity of the abdominal wall, 155
- Benign nodular lymphoid hyperplasia of the small bowel, 430 (discussed by R. J. Keller)
- Demonstration of the renal fascia, 158
- Dermoid cyst of the ovary verifying ovarian mobility during pregnancy, 423
- Distended urinary bladder impeding passage of the fetal head, 156
- Hematoma of the larynx, 145
- Hereditary onycho-osteodysplasia, 150
- Hypernephroma with massive perirenal hematoma, 439 (submitted by M. R. Shevach)
- Ischemic colitis: Presentation of seven cases, 324
- Post-traumatic arteriovenous fistula between carotid artery and ophthalmic vein, 164
- "Prune-belly" syndrome, 425
- Small bowel appearance in anaphylactoid purpura, 431
- Traumatic vertebral arteriovenous fistula, 160
- Ralph Colp Award Winner, 77
- Ramirez-Irizarry, A. A., and Bluestone, L.
- Carpal tunnel compression syndrome: Unusual case reports, 210
- Recurrent sacrococcygeal teratoma with

- rectal fistula. (Unusual Problems in Surgery), 227
- Relevance of morphology in medicine. (H. Popper), 3
- Research, medical. (Francis H. C. Crick), 178
- Respiratory paralysis induced by polymyxin B. (R. A. Levine, et al.), 380
- Reversible granulocytopenia in a patient with polycythemia vera taking nitrofurantoin; Report of a case. (S. B. Levy, et al.), 26
- Richmond, S., and Pordy, L. The occurrence of type B-Wolff-Parkinson-White conduction in the presence of right bundle branch block, 96
- Right bundle branch block. (S. Richmond and L. Pordy), 96
- Rosenstock, N., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380
- Rosenthal, Martin C. Obituary, 345
- Rubella virus
as a teratogen. (T. S. Elizan, et al.), 108
Experimental teratogenesis in ferrets using rubella virus. (T. S. Elizan, et al.), 103
- S**AMET, P., and Lister, J. W. Selected experiences with cardiac pacing, 248
- Schiffrin, Arthur. Obituary, 451
- Schneierman, S. S.
..., and Bottone, E. Aortic aneurysm infected with *Klebsiella pneumoniae*, Serotype 1: Case report, 10
..., and Feinberg, K. A. Disseminated infection by *Mycobacterium fortuitum*, 375
- Schwarz, R., et al. Peripelvic urine granuloma: Case report, 30
- Selected experiences with cardiac pacing. (P. Samet and J. W. Lister), 248
- Sever, J. L.
..., et al. Experimental teratogenesis in ferrets using rubella virus, 103
..., et al. Study of rubella virus as a teratogen in experimental animals: A short review, 108
- Severe hypoxemia in an obese patient with polycythemia vera. (E. L. Chusid, et al.), 21
- Sherry, H. S., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380
- Short-term evaluation of L-Dopa therapy in 34 patients with Parkinsonism. (R. J. Mones and T. S. Elizan), 503
- Sickle cell trait. (Sir Peter Medawar), 189
- Simon, N. Afterloading multiple irradiators for the treatment of cancer of the corpus of the uterus: A preliminary report of a new device, 443
- Small bowel appearance in anaphylactoid purpura. (Radiological Notes), 431
- Sobel, H. J., et al. Peripelvic urine granuloma: Case report, 30
- Sociology. (G. W. Beadle), 171
- Spongiblastoma Multiforme. (S. W. Gross, et al.), 123
- Spritzer, R. C., et al. Ineffectiveness of diazepam as an antiarrhythmic agent, 408
- Stats, Daniel Memorial Prize, 77
- Studies in bullous diseases: Treatment of pemphigus vulgaris with methotrexate, two patients (one with concurrent myasthenia gravis). (S. M. Peck and K. E. Osserman), 71
- Study of rubella virus as a teratogen in experimental animals: A short review. (T. S. Elizan, et al.), 108
- Sulfonyleurea. (H. Dolger, et al.), 471
- Surgery, results of. (P. Marchand), 200
- Syndrome, nephrotic. (T. Kahn, et al.), 15
- T**ACHYCARDIA, ventricular. (M. A. Nevins, et al.), 408
- Teratogenesis
experimental with rubella virus. (T. S. Elizan, et al.), 103
rubella virus as a teratogen. (T. S. Elizan, et al.), 108
- Thrombocythemia. (G. Koreman), 317
- Tolbutamide in pregnancy and diabetes. (H. Dolger, et al.), 471
- Tolins, S. H.
..., and Wagner, R. B. Pancreatic ascites. Case report: Ascitic fluid lipase utilized for diagnosis, 216
..., et al. Mesenteric vascular occlusion, 220
- Traet
biliary. (A. B. Apt and L. M. Deppisch), 48
gastrointestinal. (J. C. Cacatian and M. Kannerstein), 299
- Trait, sickle cell. (Sir Peter Medawar), 189
- Transplantation, cardiac. (D. A. Cooley), 475
- Traumatic vertebral arteriovenous fistula. (Radiological Notes), 160
- U**NIVERSITY, role in medicine. (G. W. Beadle), 171
- Unusual Problems in Surgery, A. R. Beck, L. Burrows, and J. J. Leichterling, Editors
Henoch-Schölein purpura, 65
Recurrent sacrococcygeal teratoma with rectal fistula, 227 (Beck, Leichterling)
- Use of valve homografts in cardiac surgery. (P. Marchand), 200
- Uterus. (N. Simon), 443
- V**ALVE
aortic. (P. Marchand), 200
homograft. (P. Marchand), 200
mitral. (P. Marchand), 200
pulmonary. (P. Marchand), 200
- Ventricular tachycardia. (M. A. Nevins, et al.), 408
- Vijayanagar, R., et al. Mesenteric vascular occlusion, 220

Violin, G. A., et al. Polymyxin B-induced respiratory paralysis reversed by intravenous calcium chloride, 380

WAGNER, R. B., and Tollins, S. H. Pancreatic ascites. Case report: Ascitic fluid lipase utilized for diagnosis, 216

Weisenseel, A. C., et al. Ineffectiveness of

diazepam as a antiarrhythmic agent, 408

Wolff-Parkinson-White conduction, type B. (S. Richmond and L. Pordy), 96

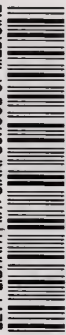
ZALUSKY, R., et al. Severe hypoxemia in an obese patient with polycythemia vera, 21



52603

JOURNAL OF THE MOUNT SINAI
HOSPITAL NEW YORK
V. 36, 1969 COPY 2

LEVY LIBRARY, MT. SINAI SCHOOL OF MEDICINE



3 4805 0901622 7